Cardiovascular and Cognitive Adaptations Following Isometric Handgrip Exercise Training in Hypertensive Adults

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Abstract

Isometric handgrip (IHG) exercise training is an effective method of blood pressure (BP) reduction in clinical and non-clinical populations. The efficacy of IHG on cardiovagal baroreflex sensitivity (cvBRS) and systemic arterial stiffness (i.e. carotid-toe pulse wave velocity (ctPWV)) is less well understood, especially in hypertensive populations who demonstrate increased arterial stiffness and decreased BRS. Furthermore, hypertension is considered an accelerated model of cognitive decline, often attributed to the effects of increased BP and arterial stiffness. This study utilized IHG (n=8) and CON groups (n=4) to examine the effects of 8-weeks of IHG training or no IHG training on arterial stiffness, cvBRS, and cognitive function in hypertensive adults. Significant group differences in SBP and ctPWV change was observed ($p<0.05$) indicating that IHG training reduced SBP and systemic arterial stiffness compared to no IHG training. Moreover, although not significant ($p>0.05$), the IHG group demonstrated an ~53% increase in BRS. Lastly, a significant difference in Trail Making Test Part A (TMT-A) time ($p<0.001$) was observed in the IHG group, suggesting that IHG training improved motor, and visual control and speed. These findings suggest that IHG training can improve systemic arterial stiffness and possibly cvBRS in a hypertensive population, in addition to the new potential for improving specific aspects of cognitive function.

KEY WORDS: isometric handgrip exercise, hypertension, cognitive function, arterial stiffness, cardiovagal baroreflex sensitivity.

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Dedication

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Table of Contents

Abbreviations

ABP	Ambulatory Blood Pressure
ACC	Anterior Cingulate Cortex
ACE	Angiotensin Converting Enzyme
ACh	Acetylcholine
ARB	Angiotensin II Receptor Blockers
BP	Blood Pressure
BPV	Blood Pressure Variability
CBF	Cerebral Blood Flow Velocity
CCA	Common Carotid Artery
CCB	Calcium Channel Blockers
CES-D	Centre for Epidemiological Studies Depression Scale
cfPWV	Carotid-Femoral Pulse Wave Velocity
ctPWV	Carotid-Toe Pulse Wave Velocity
CO	Cardiac Output
crPWV	Carotid-Radial Pulse Wave Velocity
cvBRS	Cardiovagal Baroreflex Sensitivity
CVLM	Caudal Ventrolateral Medulla
DBP	Diastolic Blood Pressure
FFT	Fast Fourier Transform
HF	High Frequency
HR	Heart Rate
HRV	Heart Rate Variability
ICA	Internal Carotid Artery
IHG	Isometric Handgrip
IMT	Intima-Media Thickness
LF	Low Frequency
LMNA	N^G-mono-methyl-L-arginine
LNAME	N^W- nitro-L-arginine methyl ester
MAP	Mean Arterial Pressure
MCI	Mild Cognitive Impairment
MMSE	Mini Mental Status Exam
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MSNA	Muscle Sympathetic Nerve Activity
MVC	Maximal Voluntary Contraction
NO	Nitric Oxide
NTS	Nucleus of the Solitary Tract
PFC	Prefrontal Cortex
PP	Pulse Pressure
PWTT	Pulse Wave Transit Time
RAS	Renin-Angiotensin System
RRI	R-wave to R-wave Interval
RVLM	Rostral Ventrolateral Medulla
SBP	Systolic Blood Pressure

SD	Standard Deviation
SV	Stroke Volume
TMT	Trail Making Test
TPR	Total Peripheral Resistance
WMH	White Matter Hyperintensity(ies)

List of Tables

List of Figures

List of Appendices

1 Chapter 1: Introduction

1.1 Study Rationale

Hypertension (resting manual arterial blood pressure (BP) ≥ 140/90 mmHg, although new guidelines exist regarding hypertension classification using automated devices is 135/85 mmHg) is now considered the leading risk factor for death in the world.[1,2] Incidence of hypertension is projected to affect 1.56 billion adults by the year 2025.[3] Conventional treatment strategies include lifestyle and pharmacological interventions which target BP reduction.[4]

Hypertension is associated with adverse changes in multiple measures of cardiovascular health such as carotid-femoral pulse wave velocity (cfPWV), arterial distensibility, heart rate variability (HRV) and cardiovagal baroreflex sensitivity (cvBRS).[5–7] Importantly, progression of arterial stiffening seen in hypertension is believed to contribute to damage in the microvasculature of the brain, which functionally manifests as reduced cognitive function.[8–13] BP and cognition have been found to demonstrate an inverse linear relationship, such that individuals with higher BP have greater cognitive impairment compared to those with lower BP.[14] Isometric handgrip (IHG) exercise training has been shown to improve resting BP and has potential to also improve arterial stiffness and autonomic function.[15] These prospective improvements in cardiovascular health may also attenuate or reverse deleterious effects on cognition associated with hypertension.[16]

Investigation into IHG training, a simple and effective BP reduction tool, has shown promising effects on several indices of cardiovascular health.[15] IHG training generally requires individuals to hold a low intensity static contraction (30% of maximum) for four

2-minute bouts, on three days per week, for a period of 8-10 weeks. This regimen consistently shows high adherence rates and significant BP lowering effects in a diverse range of populations, while requiring a lower time commitment in comparison to traditional exercise strategies.[15] Most importantly, IHG training reduces BP in medicated hypertensive adults.[17–19] However, little is known regarding additional effects of IHG training on secondary indices of cardiovascular health apart from decreased BP.[15] Hypothesized improvements included increased cardiovagal baroreflex sensitivity (cvBRS), reduced arterial stiffness (PWV, common carotid artery (CCA) distensibility) and, ultimately, improved cognitive function. As such, IHG exercise is a promising intervention with potential for improving the above factors which influence cognitive function and will be investigated in the present study.

1.2 Objectives

This study aimed to investigate several objectives surrounding cardiovascular and cognitive health in hypertensive adults.

1. To determine the effects of 8-weeks of IHG training on markers of arterial health and stiffness (i.e. BP, CCA distensibility, ctPWV, crPWV).
2. To determine the effects of 8-weeks of IHG training on measures of cardiac autonomic function (i.e. cvBRS, HRV).
3. To examine adaptations in assessments of cognitive function following 8-weeks of IHG training.

2 Chapter 2: Literature Review

2.1 Blood Pressure

Arterial BP refers to the pressure exerted against arterial walls and transiently rises and falls to meet the demands of the cardiovascular system in order to maintain a homeostatic environment.[20] Arterial BP is influenced by a combination of arterial blood volume and arterial compliance which is further affected by cardiac output (CO) and total peripheral resistance (TPR).[21] Systolic blood pressure (SBP) is defined as the outward pressure against the arterial wall when blood is ejected from the left ventricle and through the arterial system, whereas diastolic blood pressure (DBP) is defined as the arterial pressure during ventricular relaxation.[22] Mean arterial pressure (MAP), represents the mean oscillating point at which BP varies during any given cardiac cycle.[21] Pulse pressure (PP), the consequence of intermittent ventricular ejection, is simply calculated as the difference between SBP and DBP.[21–23] Additionally, TPR is calculated as the ratio between MAP and CO and represents the resistance to flow in the arterial system.[21]

Early epidemiologic studies pointed towards DBP as a stronger predictor for cardiovascular disease severity than SBP, until a paper from the Framingham Heart Study showed SBP was associated with complications linked to hypertension.[24,25] However, even more recently, epidemiologic investigations suggest that SBP is superior to DBP for predicting risk of stroke and ischemic heart disease, as elevations in SBP are associated with increased TPR.[24,26,27] In addition to SBP as a cardiovascular disease risk predictor, PP has emerged as an independent marker of cardiovascular risk and is strongly associated with cognitive impairment in hypertensive populations.[8,23,28]

In clinical practice, resting BP is most commonly measured via auscultation which requires a mercury sphygmomanometer and stethoscope placed around the upper arm and over the brachial artery respectively.[29,30] The mercury sphygmomanometer is manually inflated to 30 mmHg above the point of disappearance of the brachial pulse and slowly released at a rate of 2 mmHg/second or 2 mmHg per beat if the suspected heart rate (HR) is ≤ 60 bpm.[29] SBP is recorded as the point where pulsations are first heard upon cuff deflation.[29,30] DBP determination requires more expertise on behalf of the clinician and is recorded at the point where pulsations disappear and/or the last sound heard upon cuff deflation.[29]

While the auscultation method of assessing resting BP is most common, it has been shown to elicit a "white-coat" effect in some patients.[31] This effect describes a clinically meaningful difference between out-of-office and office BP in treated hypertensive individuals.[31] When the difference between office and out-of-office BP is ≥ 20 mmHg SBP and/or ≥ 10 mmHg DBP, white-coat hypertension is believed to be present.[32] White-coat hypertension has been shown to be minimized in situations where physicians have minimal involvement in the BP measurement.[32] As such, automated BP measuring devices have become increasingly common in clinical practice, often replacing the mercury sphygmomanometer altogether. Which is why automated BP measuring devices are now commonly used to assess hypertension status over the mercury sphygmomanometer and have a slightly lower classification value of 135/85 mmHg due to the inherent lower measured values observed with this method.[2]

Automated BP measuring devices rely upon internal algorithms which detect small pressure oscillations.[33] It is interesting to note that the oscillometric method of determining

BP actually pre-dates auscultation as it was first introduced in 1876 by Marey.[34] Unfortunately, the oscillometric method was ahead of its time as the technology required to accurately incorporate this method into clinical practice was not in place until the 1970s and 1980s when microprocessors and miniature electronic pressure sensors were developed to validate and automate measurements against gold standard measurements using intra-arterial pressures and auscultation.[33] These automated oscillometric devices calculate BP by measuring a series of small pressure pulses while the cuff pressure is consequently increased and decreased.[33] Furthermore, the amplitude of these oscillations is used to determine the SBP and DBP respectively.[33]

Automated BP aims to reduce the three most common errors associated with resting BP measurement: 1) patient related (i.e. stress associated with clinic visit) 2) observer error and 3) observer-patient interaction.[32] The white-coat effect typically observed during regular office BP measurement is almost completely abolished by use of an automated BP device.[35] When automated BP was introduced into the primary care of individuals with predominantly isolated systolic hypertension and receiving antihypertensive therapy, SBP was decreased within a range of 9-13 mmHg compared with auscultation.[35]

Automated BP devices provide an effective alternative to manual BP in that measurement is less affected by the environment (e.g. office vs. home), they provide similar information to awake ABPM devices, and they reduce the white-coat effect as previously mentioned.[32] In addition to the above recommendations for automated BP, circumstances where testing occurs at multiple sites and the same technician is unable to attend all sessions lend itself to the use of automated BP devices to reduce variation across sites.[32]

2.1.1 Hypertension

Hypertension, or chronically elevated BP, is diagnosed as the average of two resting BP measurements ≥ 140/90 mmHg when measured on at least two separate occasions by a sphygmomanometer.[36,37] Recent literature suggests when measuring and classifying BP using an automated BP device, a lower cut-off for hypertension of 135/85 is required.[2] An estimated 29.2% of individuals 20 years and older are projected to have hypertension by the year 2025; a 4% increase from the year 2000.[3] Furthermore, the estimated total number of adults living with hypertension is projected to increase by 60% from the years 2000 to 2025.[3] Of these individuals expected to develop hypertension over the coming decade, increases of 24% and 80% are predicted to occur in economically developed and developing nations respectively.[3] A recent study found that high BP has overtaken childhood malnutrition, unsafe water consumption, sanitation and hand-washing as the leading individual risk factor for death in the world.[1] Accordingly, hypertension is now widely regarded as a global health concern.[3]

Hypertension is associated with numerous adverse health-related outcomes including increased risk of cardiovascular disease such as stroke, heart failure, chronic kidney disease, and peripheral artery disease.[4] Hypertension is considered to be one of several modifiable risk factors for cardiovascular disease including sedentary lifestyle, smoking, diabetes, high cholesterol, physical inactivity and overweight/obesity.[38] The precise etiology of hypertension is unknown in approximately 90-95% of all cases and is referred to as essential hypertension.[37]

Traditional anti-hypertensive treatments involve a combination of lifestyle and pharmacological interventions. Lifestyle interventions include weight management,

reduction in dietary salt and alcohol intake, and increased physical activity.[39] Some of the most commonly prescribed anti-hypertensive medications include diuretics, beta blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), and vasodilators. Briefly, diuretics promote increased secretion of water from the body through prevention of sodium reabsorption, thereby reducing blood volume and BP.[40] Beta blockers are competitive antagonists which block norepinephrine and epinephrine receptor sites which result in decreased HR and CO, inducing a concomitant decrease in BP.[40] ACE inhibitors induce relaxation of vascular smooth muscle in arterial walls by blocking the conversion of angiotensin I to angiotensin II, thereby lowering arterial resistance and venous capacity, decreasing CO and therefore BP.[41] ARBs prevent angiotensin II from binding to angiotensin II receptors on vascular smooth muscle, thus allowing the artery wall to dilate and result in BP reduction. CCBs block calcium inflow through channels in the vascular smooth muscle and myocardium, thus increasing coronary dilation, decreasing myocardial contractility, and decreasing peripheral resistance.[40] Vasodilators induce BP reduction via a reduction in sympathetic tone to vascular smooth muscle.[40] While the mechanism of action of each medication is variable, the goal is generally to provide a stimulus which reduces vasoconstriction, or the degree of activation of the vascular smooth muscle cells within the arterial walls. Multiple classes of anti-hypertensive medication are often utilized as nearly two-thirds of hypertensives are unable to control resting BP to within clinical target ranges using a single anti-hypertensive medication.[42]

Anti-hypertensive medication is effective in only 53% of hypertensive individuals.[43] This may be a result of poor adherence to medication regiments, perhaps due to side-effects

associated with medications. Non-adherence to anti-hypertensive medication is associated with worse BP control and adherence usually declines over time with an estimated 42% of newly diagnosed hypertensive individuals ceasing to continue with their medication within 1 year of starting treatment.[44,45] Aerobic and resistance exercise are often recommended as a method of BP reduction however, not knowing how or what to do and lack of motivation are often cited as barriers preventing individuals from participating in exercise to observe these adaptations.[46] Thus a simple, time efficient and effective method of BP reduction is warranted to help combat the low rates of hypertension control.

2.2 Arterial Stiffness

The cardiovascular system is comprised of the heart, arteries, and veins, and is responsible for distributing blood throughout the body to meet metabolic demands. The arterial system functions as a conduit which transports oxygenated blood and dampens pulsatile flow generated through the intermittent ejection of blood from the heart.[47] One of the most clinically relevant arteries is the aorta which, in healthy individuals, is capable of significant levels of distension to propagate pulse waves distally along the vessel length.[48,49]

Each segment of the arterial system is comprised of elastin, collagen, and vascular smooth muscle. Elastin provides reversible extensibility during mechanical loading and unloading of arteries throughout the stages of the cardiac cycle, whereas collagen prevents arterial wall failure at high pressures.[50] Vascular smooth muscle minimally influences behaviour of large elastic arteries such as the aorta, but in peripheral resistance arteries, vascular smooth muscle cells are primarily responsible for spontaneous vasomotor changes in diameter and stiffness.[51–53] This, in addition to greater collagen concentrations in small

peripheral arteries, contributes to increased peripheral arterial stiffness in comparison to the central arteries.[49,52]

Arterial composition is not homogenous throughout the arterial tree in that central arteries contain higher elastin levels compared to peripheral arteries.[23,54] Likewise, this concentration is not static throughout the lifespan and across the BP spectrum.[49] As elastin is broken down due to aging or BP induced adaptations, increased collagen is deposited to maintain the structural integrity of the arterial wall, thus resulting in a shift of the arterial mechanical properties towards increased stiffness.[23,49]

2.2.1 Central Pulse Wave Velocity

Stiffness of the large central arteries (i.e. aorta) is most commonly measured using the gold standard carotid-femoral pulse wave velocity (cfPWV).[48] cfPWV measures the speed at which a pressure waveform propagates along a segment of the arterial tree; the stiffer the vessel, the greater the PWV. It is calculated as:[48]

$$PWV = \Delta D / \Delta T$$

where ΔD is the distance (metres) between measurement sites and ΔT represents the pulse wave transit time (PWTT) (seconds).[48]

When blood is ejected from the left ventricle of the heart, a pressure wave is generated against the arterial wall which travels at a given PWV along the arterial tree in direct proportion to the elastic properties of that vessel segment. In healthy arterial systems, the pulse wave propagates at a lower velocity due to pulsatile energy being stored in the elastic arterial wall to a greater extent than in older individuals and those with hypertension whom have stiffer arteries.[7] Progressively higher BP is associated with increased PWV at

any age (Figure 2.1). It is impossible to extrapolate segmental arterial properties to the entire arterial tree as no segment has identical viscoelastic properties and concentrations of elastin, collagen, and vascular smooth muscle; thus greatly influencing the PWV of any given artery.[48]

The most clinically relevant measure of PWV is cfPWV.[48] cfPWV considers the time of arrival of the forward pressure wave to proximal (carotid) and distal (femoral) sites relative to the R-wave of the cardiac cycle, which corresponds to ventricular contraction and blood ejection from the heart. The PWTT corresponds to the time in seconds it takes the pressure wave to propagate from the heart to the locations being measured, in this case, the common carotid (CCA) and femoral artery. The time of arrival is identified by the systolic upstroke of the pressure wave at the arterial site. PWTT is determined for both the proximal and distal sites from which the difference in time is calculated (distal-proximal).[48,55] Similar principles apply with calculating distance (metres) between sites (distal-proximal). While PWV is well accepted, several shortcomings exist which may confound the measure. Distance is most commonly estimated by measuring the surface distance on the body relative to the sternal notch using an inelastic tape measure.[48] Additionally, profound adiposity causes issues regarding ability to obtain certain waveforms accurately in addition to distance between measurement sites as body shape may influence the outcome measurement. No universally accepted distance measurement has been developed.[48]

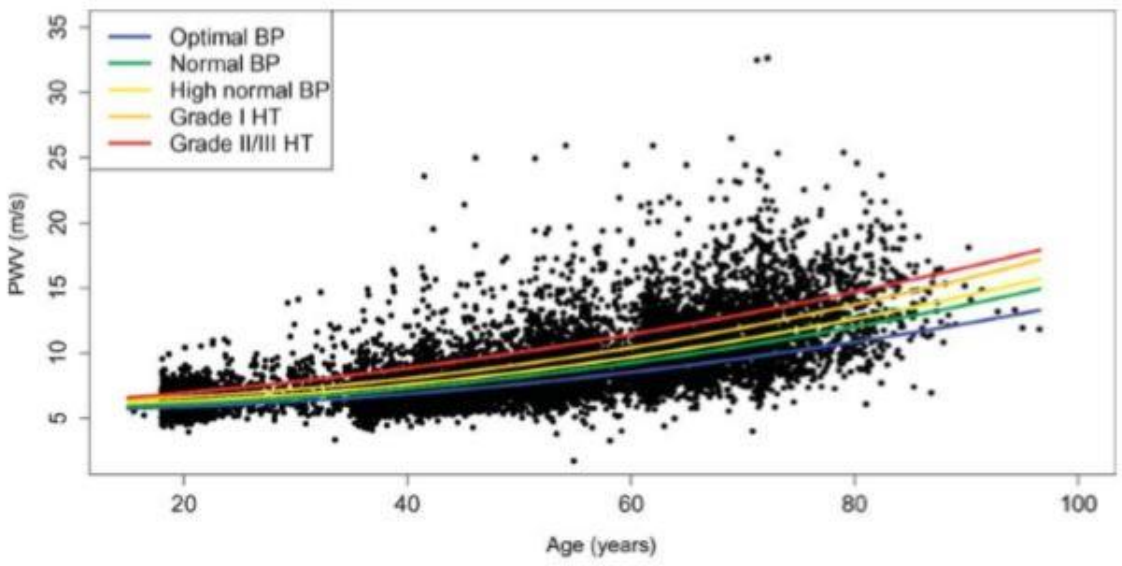


Figure 2.1 *Influence of blood pressure status on PWV across the lifespan*. Increased cfPWV is observed at any age in individuals with progressively higher BP category. Taken from Boutouyrie.[7]

Central elastic arteries are most prone to stiffening; this relationship was identified as early as 1922 by Bramwell and Hill in their Nobel Prize winning study, which pioneered the measurement of PWV in humans.[56] Normative values for cfPWV have since been established in a large European cohort study across 13 centres and in 11,092 participants.[7] Mean cfPWV varied from 6.2 m/s in young adults (≤30 years) to 10.9 m/s in older adults (≥70 years) with a proposed threshold of 12 m/s associated with significant clinical outcomes, although this study did exclude individuals with specific adverse cardiovascular conditions in order to achieve a relatively healthy sample (i.e. diabetes, dyslipidemia, and anti-hypertensive therapy).[7] In fact, this large cross-sectional study determined that at any age the presence of elevated BP is associated with increased cfPWV. This relationship was identified with BP ranging from optimal (< 120/80 mmHg) to grade II/III hypertension (≥ 160/100 mmHg).[7]

2.2.2 Peripheral Pulse Wave Velocity

As previously mentioned, elastic central arteries are most prone to increased stiffening with increased age.[49,56] This trend is not as significant in peripheral arteries due to the inherent arterial compositional differences in peripheral and central arteries. A Framingham Offspring cohort study investigated the effects of age on cfPWV and peripheral PWV (carotid-brachial and carotid-radial) in adults free of clinical cardiovascular disease.[57] Age-related increases in cfPWV but not peripheral PWV was identified in this study, although on average, up to age 50 years, peripheral stiffness was higher than cfPWV.[57]

2.2.3 Local Arterial Stiffness

Changes in arterial diameter occur as the forward pressure wave exerts an outward force against the arterial wall. Distensibility, or the relative change in vessel diameter for a given change in pressure, is a local measure of arterial stiffness and elastic properties.[58] Distensibility can then be computed as the difference between cross-sectional arterial diameter (ΔCSA= maximum – minimum CSA) divided by the product of PP and the minimal cross-sectional area:[58]

$$Dist\ (mmHg^{-1}) = \Delta CSA/(PP * CSAmin).$$

Distensibility is most commonly measured non-invasively using ultrasonography in the B-mode setting with a high-frequency linear array transducer.[48] Measurement at the CCA is made 1-2 cm proximal to the carotid bifurcation. Calculation of distensibility requires applanation tonometry to non-invasively determine local PP at the level of the CCA or use of a transfer function which adjusts peripheral PP to the level of the CCA.

The most dominant physiological processes known to affect arterial distensibility are aging and hypertension.[6,59] In 1994, the first non-invasive study of the CCA pressure-distensibility curve was conducted.[6] From this study, it was found that at any given BP, CCA distensibility was not reduced in hypertensives compared with age and sex matched controls. In essence, the curves overlapped with the hypertensives having lower CCA distensibility at a higher BP. However, the compliance-diameter curve was shifted towards higher levels in the hypertensives, suggesting hypertension may be a result of both increased pressure and diameter. Thus, hypertension-induced changes in CCA structure plays a minimal role in the observed decreased distensibility and compliance.[6] This population of hypertensives included never treated, chronic hypertensives, or those withdrawn from anti-hypertension medication for a period of 6 months prior to the study; this permitted the maximum likelihood of identifying structural changes and strengthens the principal findings of the study.[6] In contrast, SBP, MAP, and PP have been found to be inversely related with CCA distensibility, with PP providing the strongest association in a population of normotensives and hypertensives.[60] This association was identified across a wide range of BP values including those below clinical hypertension. Additionally, hypertension affects the functional properties of large centrally-located arteries more so than the smaller peripheral arteries.[59] Generally, when hypertension is present, the effects on distensibility are more pronounced at any age.

2.2.4 Intima-Media Thickness

Arteries are composed of three distinct layers: intima, media, and adventitia.[61] The intima is the innermost layer of cells which lies between the lumen and media layer of arteries.[62] The thickness of this layer, or intima-media thickness (IMT), changes with increasing age

and cardiovascular risk factor presence.[63] Due to its accessible location via ultrasonography, researchers are able to measure IMT and investigate its clinical relevance in clinical and non-clinical populations (Figure 2.2).

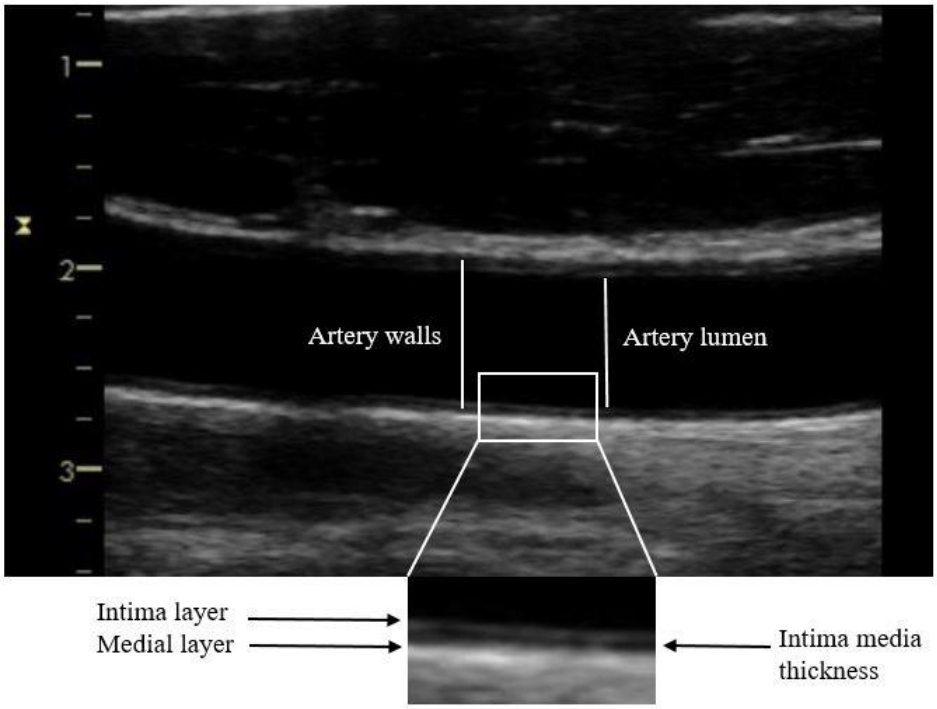


Figure 2.2 *Ultrasound image of the CCA demonstrating arterial landmarks used for distensibility and intima-media thickness calculations.*

IMT can be seen as a double line pattern on a vessel in a longitudinal view and can then be used for risk stratification and as end points in observational studies. The parallel boundaries are the lumen-intima and media-adventitia interfaces respectively.[64] IMT is frequently measured at the CCA due to low likelihood of plaque formation in comparison to the internal carotid artery (ICA), a secondary site of IMT measurement. Anatomically speaking, the carotid bifurcation and ICA are more prone to plaque formation than the CCA which is more accessible to researchers.[64] Therefore IMT measurement of the CCA is preferred over ICA.[64] Increased IMT is associated with a number of cardiovascular and

cerebrovascular conditions including myocardial infarction, coronary artery disease, and stroke.[65] As such, assessing IMT at the CCA is warranted when considering local arterial stiffness and systemic effects of stiffness on cardiovascular and cerebrovascular health.

2.3 Autonomic Regulation of Heart Rate and Blood Pressure

The autonomic nervous system is predominantly responsible for regulation of HR and BP through the sympathetic and vagal nervous systems which operate antagonistically, in most circumstances.[66] Cardiac sympathetic stimulation via nerve fibres in the upper thoracic and lower cervical segments of the spinal cord decreases R-R interval (RRI) (time between consecutive R-waves of cardiac cycle). Increased vagal outflow via nerve fibres in the nucleus ambiguous of the medulla oblongata increases RRI.[67] As such, RRI is dependent on the ratio of sympathetic to vagal stimulation.[68] RRI and BP are influenced by the autonomic nervous system and are linked by several feedback mechanisms, namely the cardiovagal and sympathetic baroreflexes, chemoreflex, endogenous vasoconstrictor release and conservation of salt and water by the renal system.[61] This thesis will focus on the cardiovagal baroreflex and its effects on beat-by-beat RRI and BP modulation. The arterial baroreflex is a negative feedback loop responsible for preventing large fluctuations in beat-by-beat BP.[67]

2.3.1 Arterial Baroreflex

Pressure sensitive baroreceptors embedded in the walls of the aortic arch and carotid sinus detect changes in arterial distension.[69–71] Barosensory afferent nerves transmit this signal to neurons of the nucleus of the solitary tract (NTS) within the medulla oblongata via the glossopharyngeal (cranial nerve IX) and vagus nerve (cranial nerve X) which innervate the carotid sinus and aortic arch respectively.[67] The arterial baroreflex is critical for

maintaining BP homeostasis to meet the body's demands. This task of beat-by-beat regulation is modulated by two different pathways, the sympathetic and cardiovagal baroreflexes (see Figure 2.3). Each pathway responds to the same stimulus of mechanical deformation of the arterial wall which is induced by changes in arterial pressure. Subsequent rapid adjustments in BP and RRI are due to mediation of the vagal and sympathetic components of the reflex arc which are under dynamic neural control.[67,72]

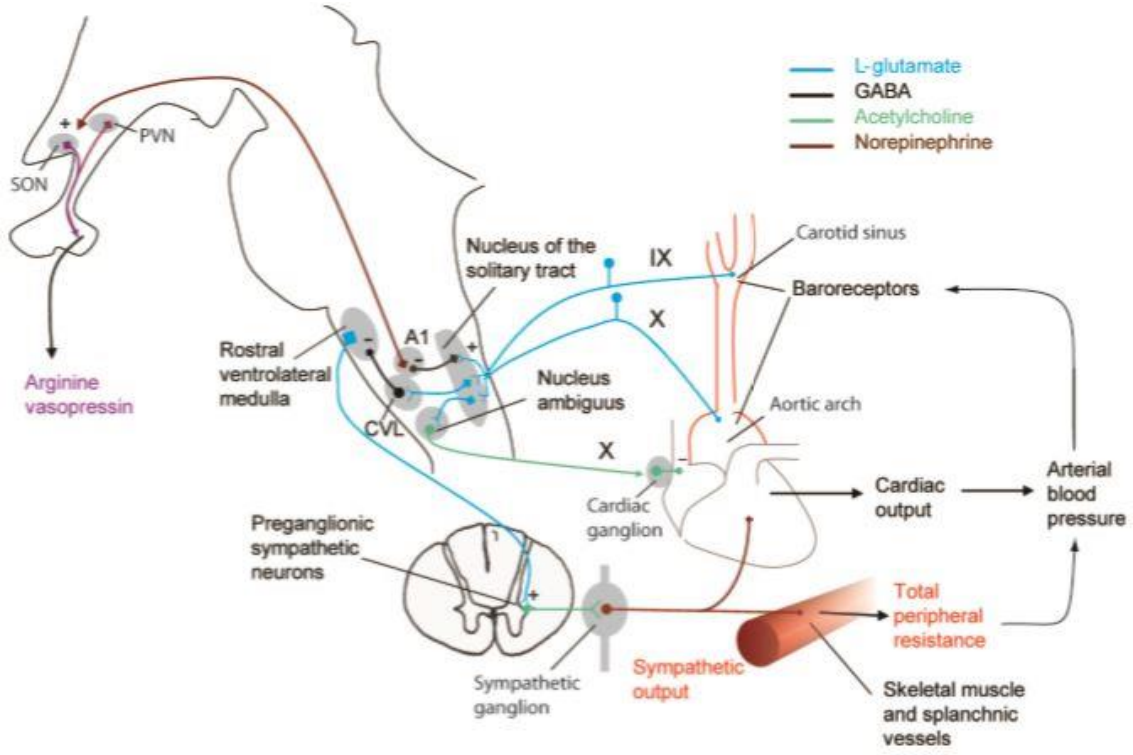


Figure 2.3 *Organization of the sympathetic and cardiovagal baroreflex pathways*. Taken from Benarroch.[67]

In the brainstem, the arterial baroreflex differentiates into two branches, the sympathetic and cardiovagal baroreflex. The sympathetic branch involves neural projections from the NTS to neurons of the caudal ventrolateral medulla (CVLM) which respond with inhibitory signals to neurons of the rostral ventrolateral medulla (RVLM).[73]

These inhibitory signals are sent to the sympathetic ganglia via acetylcholine (ACh). The RVLM is a primary regulator of sympathetic activity.[67,74] Therefore, when BP is elevated and the baroreceptors are activated, the NTS activates the CVLM, which in turn inhibits the RVLM. This results in a reduction of sympathetic activity leading to an increase in RRI (decrease in HR), decrease in cardiac contractility and vasodilation of peripheral arteries (i.e. decreased TPR) to reduce BP.[67] The reciprocal is true for low BP which reduces the firing rate to the NTS, in turn increasing sympathetic outflow to consequently cause a rise in BP.

The cardiovagal baroreflex originates within the NTS where the neurons of the NTS synapse with vagal preganglionic neurons of the nucleus ambiguous.[67] Cholinergic neurons extend to the cardiac neurons (via vagus nerve branches) where they terminate in the sinoatrial and atrioventricular nodes of the heart. At these termination points, ACh is released, thus producing a negative chronotropic effect (decrease in HR).[68] Therefore, when an increase in BP, or increased wall distension is detected by the arterial baroreceptors, the firing rate to the NTS is increased which results in decreased sympathetic outflow and augmented vagal outflow.[67]

The timing of this reflex loop differs depending on whether sympathetic or vagal stimulation is required as the difference in time delays between systems is substantial.[75] Vagal activation is almost immediate and requires 200-600 milliseconds (ms), whereas sympathetic activation requires a 2-3 second delay.[68] Thus, beat-by-beat control of RRI is predominantly controlled by vagal activity.

2.3.2 Baroreflex Sensitivity

Cardiovagal baroreflex sensitivity (cvBRS) quantifies the efficiency of the arterial baroreceptors' ability to regulate beat-by-beat RRI and BP. cvBRS is defined as the change in RRI ms per unit change in SBP (mmHg).[72] Techniques of BRS assessment in humans have been extensively researched and include invasive and non-invasive methods. All methods require continuous electrocardiogram and arterial pressure recordings in order to regress concurrent changes in RRI against changes in BP. The slope of this relationship is an expression of the cvBRS and represents the increase in RRI (ms) per millimetre rise in mercury.[68] When regressed against each other, the steeper the slope of the RRI-BP relationship, the greater the cvBRS value.[68,76] Normative cvBRS values have been established and are known to range from 3-34 ms/mmHg depending on age, sex, and health status, although higher and lower values are possible.[68,77] Reduced cvBRS ($\leq$ 3 ms/mmHg) is associated with cardiovascular disease and death in patients following myocardial infarction.[68]

2.3.2.1 Pharmacological Methods

Early pharmacological methods designed to quantify cvBRS relied upon external perturbations that elicit changes in RRI and BP. One such method requires an intravenous injection of angiotensin II and saline to activate arterial baroreceptors.[78] Rapid injection of angiotensin II elicits an abrupt rise in BP accompanied by cardiac slowing (increased RRI). Use of angiotensin II to induce this reflex was questioned as the cardiac response may not be of complete reflex origin (i.e. late tachycardia was likely a result of central sympathetic stimulation).[76] The same research group then used a similar yet more selective pressor agent, phenylephrine, which does not induce direct effects on cardiac contractility and the

central nervous system.[76] Infusion of phenylephrine is performed in a graded manner until SBP increases 20-30 mmHg, an indication of an optimal dosage.[68] Since these early investigations, phenylephrine has been commonly used in laboratory based settings to assess cvBRS and is referred to as the Oxford method in respect to the institution from where the researchers originated. Further iterations of the Oxford method used bolus infusion of sodium nitroprusside and phenylephrine to induce a greater reflex response.[79,80]

2.3.2.2 The Neck Chamber Method

Neck chambers were first described by Ernsting and Parry in 1957 as a means to stimulate the carotid baroreceptors without the use of pharmacological interventions, which are known to not be entirely reflex in origin.[76,81] This method requires a chamber which is placed around the individual's neck, resting between the upper thorax and neck. This chamber either produces positive or negative pressure pulses for 5-second, generally performed 2-4 times at pressures from -40mmHg to +80mmHg. Numerous chamber designs have emerged since the method was first introduced, although the underlying physiological mechanisms induced by each design remain unchanged.[82] The carotid baroreceptors respond to increases in chamber pressure with a reflexive decrease in RRI; similarly, decreases in chamber pressure elicits reflexive increases in RRI.[68,83]

Neck chamber methods are advantageous for the assessment of cvBRS in that they allow for concurrent changes in RRI and BP by the carotid baroreceptors.[68,82,83] Additionally, neck chamber methods allow for baroreceptors to be assessed over a larger range of pressures in comparison to pharmacological methods. Furthermore, neck chambers permit the investigation of carotid baroreceptor activation under unique experimental conditions (i.e. exercise) which are otherwise not feasible with

pharmacological interventions. However, this methodology only permits the assessment of the carotid baroreceptors and neglects those of the aortic arch.[67,70] Moreover, it is unknown precisely how much of the applied pressure is transmitted directly to the carotid baroreceptors, with studies reporting values ranging from 64-100% transmission.[84,85] Thus, researchers have since pursued less intrusive methods of cvBRS assessment which require no additional equipment, and rely exclusively on basal variability in RRI and SBP.

2.3.2.3 Spontaneous Methods

Non-invasive, computer based methods of cvBRS assessment include sequence analysis (time domain) and spectral analysis (frequency domain). Time and frequency methods allow for observation of naturally occurring beat-by-beat BP and RRI fluctuations, thus enabling investigators to evaluate cvBRS without added devices or pharmacological agents in a time and cost effective manner. Importantly, due to the nature of the measurement itself, spontaneous methods allow for examination of the baroreflex as a closed-loop system.[83] Furthermore, spontaneous analysis is well suited for detection of impaired cvBRS compared with traditional methods which often lead to conclusions of "normal" results.[86] In this sense, sequence and spectral analysis may be considered superior to pharmacological and mechanical manipulation methods at detecting early risk of morbidity and mortality in at-risk populations.[83,87]

The sequence method uses the time domain while allowing for separate identification of "up" and "down" sequences of SBP and RRI. Sequence analysis allows for computer identification of sequences of three or more consecutive beats characterized by a progressive rise or fall in SBP and subsequent lengthening or shortening of RRI.[87] Typical accepted correlations of change in SBP and RRI are those of 0.85, which

demonstrates a high specificity. Most commonly, changes must be ≥1 mmHg and 5-6ms for SBP and RRI respectively to be included in regression analysis.[87] The average slope between the regression line of the SBP and RRI changes can then be taken as an index of cvBRS.

Spectral analysis, uses the modulus, or gain, of the transfer function between variations in SBP and RRI in the low frequency (LF) band (0.04-0.15 Hz) for quantification of cvBRS.[88] The LF band is shown to be independent of the respiratory or high frequency (HF) band (0.15-0.4 Hz).[89] Segments containing 128-1024 beats are required for analysis and are further quantified by discrete Fast Fourier Transform (FFT) of the SBP and RRI LF spectral powers.[83] FFT incorporates all data in the spectral distribution and is commonly used on large samples due to its reproducibility and high processing speed.[90]

Specifically, transfer function analysis in the LF band is highly correlated to traditional phenylephrine and Oxford method derivatives.[88] This method can be considered superior to phenylephrine for several reasons, chief among them being the non-invasive nature of the measure which relies on spontaneous oscillations in BP and RRI. Secondly, repetitive phenylephrine injection should be avoided due to potential modification of vascular smooth muscle tone in the walls of the CCA and aortic arch.[83] A third advantage is that cvBRS values are not dependent upon the measurement method itself. One of the most important limitations to the Oxford technique is that significant associations are not always seen in individuals with autonomic impairment, whereas transfer function analysis is better suited for the detection of imbalances than pharmacological methods.[88] For the aforementioned reasons, cvBRS will be assessed using spectral analysis in the LF band (0.04-0.15 Hz) for the present thesis.

2.4 Isometric Handgrip Exercise Training

Isometric exercise involves sustained muscle contraction with no change in length of the working muscle group.[91] Human models are unable to confirm pure isometric contractions, thus it is generally accepted that static contractions involve minimal change in muscle length. Isometric hand grip (IHG) exercise is widely used in clinical settings and involves a sustained low to moderate intensity contraction of the forearm musculature against a handheld device which provides feedback on contraction intensity. IHG exercise has gained attention due to the impressive hypotensive effects observed following a period of training and has now been recommended by the American Heart Association as a class IIB, evidence level C treatment strategy for BP management as an adjunct therapy for BP reduction.[92,93] This classification was assigned to IHG training based on the limited populations investigated to date and having only received a consensus statement from experts in the field. The American Heart Association and Canadian Hypertension Education Program both recommend IHG training as a key lifestyle therapy for hypertensive individuals.[92,93]

Early on, researchers observed an association between isometric contractions in the workplace and low BP.[94] This initial finding led to research into the potential mechanisms responsible for the hypotensive response to a hypertensive stimulus. When the acute effect of IHG exercise was formally investigated, it was determined that IHG induces modest increases in SBP and DBP (17 and 16 mmHg respectively) in accordance with increased HR and muscle sympathetic nerve activity (MSNA).[95,96] Researchers have since developed formalized training regimens that have been proven effective at lowering resting BP in a

range of populations including young normotensive men and women, pre-hypertensive adults, and medicated hypertensive adults.[17–19,96–98]

Percentage of maximal voluntary contraction (MVC) is a simple prescription for training intensity of IHG contraction. Percent MVC requires individuals to perform a single maximal contraction of the involved limb producing a specific force output, which is then adjusted to a particular training intensity. Several studies have sought to elucidate the effects of training intensity on the hypotensive response to isometric training. An 8-week isometric bilateral leg training study in healthy males was performed in which one group exercised at 30% of subject specific maximal electromyographic output (similar to % MVC) and the second group exercised at 50%. There were no differences in $\dot{Q}$, stroke volume (SV) or TPR between groups following the 8-week training period demonstrating that 30% and 50% EMG produced similar training responses, however the 50% MVC group did achieve results at a faster rate than the 30% MVC group.[17,95,97] As a result, subsequent studies have relied heavily upon 30% MVC as the desired training intensity.

Training frequency has also been a subject of investigation in determining optimal dosage to elicit BP reductions. In a study of young normotensive women using an identical IHG training program, groups trained 3 days per week (low frequency) or 5 days per week (high frequency), each for 8 weeks at 30% MVC.[97] The high frequency training group experienced significant reductions in resting SBP at 4 weeks of training, whereas the low frequency group demonstrated significant SBP reductions at 8 weeks. Nevertheless, the study concluded that SBP reductions were equivalent to 6 mmHg in each group by the 8-week mark.[97] This suggests training at higher frequency (i.e. 5 days per week) results in a faster rate of adaptations than training at low frequency (i.e. 3 days per week), although no

difference is observed between groups by the 8-week mark. However, it is believed and recommended that using low-frequency training will result in higher retention rates and be an easier protocol for participants. Therefore, in line with 30% MVC contraction intensity, a frequency of 3 training days per week for a period of 8 weeks will be used.

Furthermore, BP reductions of greatest magnitude are typically observed in hypertensive populations, those with highest pre-training BP, and those with the greatest cardiovascular reactivity.[95,98–100] Interestingly, medicated hypertensive patients do not consistently experience BP reductions seen in other populations.[18,19,101] It has been postulated this may result from interacting effects of pharmacotherapy and the mechanisms by which BP reductions occur via chronic IHG exercise. Thus, IHG training is becoming an effective method of BP management in hypertensive individuals, although the mechanisms remain speculative.

IHG training studies to date have emphasized measuring resting seated BP, similar to that which is assessed in clinical settings, however ambulatory BP monitoring over a 24 hour period is considered the gold standard method for risk prediction associated with BP and is commonly used to assess Circadian patterns in individuals with suspected hypertension and white-coat hypertension.[102,103] One study to date has assessed the influence of IHG training on ambulatory BP which demonstrated no change in BP following a training period of 8-10 weeks in a population of controlled (BP $\leq$120/80 mmHg) hypertensive individuals.[99] Thus, the robustness of IHG training on BP measured out of office (e.g. ambulatory BP) is currently unknown and requires future research.

2.4.1 Neural Control During Isometric Exercise

Isometric contractions induce an exercise response which is controlled by two mechanisms: 1) central command (CC) and 2) exercise pressor reflex (EPR).[104] CC is a feedforward mechanism which sets basic patterns of motor activity (i.e. signals muscle contraction) and drives the cardiorespiratory activation patterns associated with exercise.[104] CC activation results in vagal withdrawal and sympathoexcitation of HR.[105] EPR is governed by the mechanoreflex (MR) and metaboreflex (MB). MR refers to the feedback control mechanism which is driven by intrinsic factors of the muscle itself.[104] Mechanical compression of musculature results in blood flow occlusion and the subsequent accumulation of metabolites which activate the muscle MB.[106] The MB is activated as metabolites accumulate due to insufficient blood flow from working muscles during contraction and thus, the MB increases vasoconstrictor sympathetic activity which acutely increases TPR and BP.[106]

Acute bouts of dynamic and isometric exercise increase MAP, although isometric exercise does so in a progressive manner, resulting in considerably greater increases in MAP than dynamic exercise.[105] A population of particular interest are hypertensive adults whom demonstrate an exaggerated response in MAP and MSNA to an acute bout of IHG exercise compared with normotensive adults.[107] As such, it is hypothesized that the metabolic component of the EPR may be overactive in hypertensive adults compared to normotensive adults.[107] In response to acute bouts of IHG, carotid baroreflex gain has gone unchanged following 35% MVC and during a period of post-exercise blood flow occlusion.[108] However, these findings are limited to the carotid baroreceptors only as the

study utilized neck suction and pressure to elicit the changes in BP to measure carotid baroreflex function.

2.4.2 Mechanisms of Action

Thus far, researchers have only hypothesized around the physiological adaptations responsible for reduced arterial pressure observed with IHG training. Common theories involve increased bioavailability of nitric oxide (NO) and thereby reductions in arterial stiffness, reduced MSNA, and improvements in autonomic function.[15,98,109,110]

2.4.2.1 Changes in Arterial Function and Stiffness

Blood flow to working muscles is reduced and/or occluded during sustained isometric contraction and the degree of reduction is dependent upon contraction magnitude.[91] Importantly, when the contraction is released, shear stress of the forward pressure wave stimulates release of paracrine substances such as NO from the endothelium.[111] Shear stress upregulates NO synthase to increase release of endothelium-derived NO, a potent vasodilator which can reduce short-term arterial stiffness and BP[112]; thus resulting in an acute hypotensive response. Repeated exposure to shear stress is thought to contribute towards improving basal NO bioavailability and bioactivity which may in turn be partially responsible for BP reductions observed following a period of IHG training.[111] NO mediated endothelial reactivity to shear stress can be assessed by flow-mediated dilation (FMD) testing, which involves hyperemic response to local limb blood flow occlusion.[113] FMD allows for evaluation of arterial diameter and is most commonly performed on the brachial artery. IHG training has been shown to improve vascular reactivity of the brachial artery in medicated hypertensives but not consistently in normotensives.[109,114,115] Substantial improvements in endothelial dilation were noted in the trained limb of medicated

hypertensive individuals only, suggesting endothelial adaptations may be local as opposed to systemic.[109]

Under basal conditions, the NO synthase inhibitor N^G-mono-methyl-L-arginine (LMNA) has been investigated in rats and humans.[112,116] Following acute saline and LMNA infusion, pressure independent increases in cfPWV, equivalent to approximately 8 years of aging, were detected in healthy men.[112] Similarly, acute and chronic infusion of an NO inhibitor, N^W-nitro-L-arginine methyl ester (L-NAME), in rats has been shown to increase aortic stiffness independent of changes in BP.[116] Chronically, reduced NO bioavailability may lead to structural modification by which arterial stiffness is increased.[116] Thus, an intervention thought to stimulate NO bioavailability (i.e. IHG training) may reduce central arterial stiffness in large arteries such as the aorta and its main branches in populations with already elevated central arterial stiffness such as hypertensive adults. The above findings support the idea that focus should shift towards effects of NO on large central arteries as opposed to smaller peripheral arteries and endothelial function in peripheral vessels such as the brachial artery, especially considering the dominant BP buffering effect of the large central arteries.[117]

2.4.2.2 Changes in Autonomic Function

Autonomic adaptations have also been suggested to occur with IHG training. Several studies have investigated autonomic adaptations following IHG training with mixed results.[97–99,101] A possible synergistic effect of good BP control through pharmacotherapy and age may contribute to limitations in the ability to consistently identify improvements in autonomic function.[99]

Early research into the association of IHG training and autonomic function was performed in hypertensive men and women, most of whom were medicated.[98] Significant reductions in SBP and MAP following IHG training were paralleled by a significant decrease in LF and increase in HF area of both HRV and BPV, along with non-significant decreases in both LF/HF ratios. These findings suggest that IHG training decreases sympathetic and increases vagal modulation of HR.[98] In contrast, no adaptations were observed in HRV for a population of well controlled (~115/68 mmHg) hypertensive adults.[99] In a similar population of well controlled medicated hypertensive adults, 8 weeks of IHG training induced a small BP reduction (~5 mmHg) and did not alter traditional time and frequency domain HRV data seen by Taylor et al..[101] However, non-linear HRV analysis of heart rate complexity and predictability such as sample entropy, and fractal scaling distance scores were improved, which suggests improved cardiac vagal function following IHG training.[118,119] Moreover, no changes in linear or non-linear HRV measures following IHG training were observed in healthy young adults, making the HRV adaptations in IHG training unclear.[97] The variances observed in the above studies may be attributed towards level of BP control and effectiveness of the prescribed medications. Specific classes of BP medications target neural pathways involved in the HR reflex arm of the baroreflex and may have already exerted theoretical maximal effects on autonomic adaptations in HRV.[5,99]

Overall, the findings to date are equivocal and suggest that traditional measures of autonomic function (e.g. HRV) are not consistently improved with IHG training, although potential for improvement exists following training in populations with autonomic dysfunction, most notably hypertensive adults. However, the major limitation of relying on

HRV as a measure of autonomic function is the inherent variability in the measure itself. Possible secondary indices of autonomic function to investigate include BPV, MSNA, and BRS. No study to date has utilized IHG training to examine whether the cardiovagal baroreflex is altered following IHG training as it is the primary system responsible for short-term BP and RRI modulation (i.e. BRS).

2.4.2.3 Changes in Muscle Sympathetic Nerve Activity

Reduction in vascular sympathetic tone and/or MSNA may be associated with BP reductions attributed to IHG training.[120] However, a study in healthy young adults was unable to identify an association between arterial pressure reductions and changes in MSNA (measured at the peroneal nerve) in response to 5 weeks of IHG training, suggesting that reduced arterial pressure does not necessarily require a concomitant reduction in MSNA.[96] The lack of association may be related to young adults displaying lower BP and MSNA in comparison to hypertensive populations known to demonstrate higher levels of both variables. It is unknown in this study whether sympathetic activity to vascular beds in other regions was affected through the training and contributing towards the reduction in BP.[96] Alternatively, the training stimulus may not have been sufficient in young adults to effectively lower BP and MSNA to the same extent as in hypertensive populations.

2.5 Association Between Cognitive Function and Hypertension

2.5.1 Global Cognition

Studies investigating cardiovascular health and cognition have been severely limited by their selection of cognitive assessment, namely an overreliance on a single test of cognitive function, the Mini Mental Status Exam (MMSE).[8] Studies have favoured the MMSE due to its ability to detect mild cognitive impairment (MCI) and dementia.[121] Unfortunately,

the MMSE is better suited for the detection of MCI and dementia than as a strict indicator of global cognitive function.[121,122] A test which is proposed to possess an improved ability to detect impairments in global cognition is the Montreal Cognitive Assessment (MoCA).[122] The MoCA evaluates multiple cognitive domains including executive function, attention, orientation, language, verbal memory, and visuospatial memory to provide a more complete picture of global cognitive function than the MMSE.[122] When compared with the MMSE, the MoCA has greater sensitivity in identifying MCI in community based older adults and is regarded for its widespread applicability to both healthy and at-risk populations.[122] MoCA scores have been associated with age and education levels, but not sex in an ethnically diverse population based cohort.[123]

2.5.2 Executive Function

Executive function is an umbrella term describing the ability to manage cognitive processes such as working memory, task switching, planning and execution. Successful performance on tasks of executive function require a combination of attention and memory.[124] Executive function and several subdomains are commonly tested for by an array of assessment tools, namely the Trail Making Test Parts A and B (TMT-A and TMT-B).

The TMT-A provides information on baseline visual and motor speed while the TMT-B requires increased cognitive demand due to task switching.[125] However, the increased trail length and perceptual variations between TMT-A and TMT-B have led researchers to question whether performance differences are due to executive function or simply a consequence of the task itself. Arbuthnott and Frank (2000) investigated several derivations of TMT-A and TMT-B scores in a healthy population and identified that executive function can be specifically determined using the ratio of TMT-B to TMT-A

(TMT-B/A).[125] Many studies examining arterial stiffness and the TMT have neglected to use the TMT-B/A as a more direct assessment of executive function.[126–128]

2.5.3 Verbal Fluency

Verbal ability and verbal fluency are differentially affected by aging and clinical conditions comparatively. Verbal ability appears to be a crystallized skill which is unaffected by age whereas verbal fluency requires significantly greater executive ability to initiate and maintain effort to a directed task.[129] Verbal fluency tests assess verbal ability via two aspects 1) lexical access ability, which refers to the ability to retrieve grammatical representations of sound from the mental lexicon and 2) executive control ability, or the ability to regulate thoughts and direct attention towards a specific goal upon request.[130] In order to be successful, individuals must possess the ability to retrieve appropriate words from their mental lexicon, in addition to avoidance of word repetition.[131]

In clinical practice, several studies have utilized verbal fluency tests in hypertensive populations and examined the association with distinct cardiovascular variables. Poels et al. assessed category fluency in healthy older adults and found cfPWV was associated with performance on this test.[132] In contrast, Zhong et al. assessed letter fluency and were unable to find an association with cfPWV in a predominantly hypertensive population.[127] A recent study conducted by Spinelli et al. investigated the relationship between several cognitive assessment scores, including verbal fluency tests, and hypertension.[133] The study concluded that hypertensive individuals with poor ambulatory blood pressure (ABP) control displayed reduced letter fluency scores than those with good ABP control.[133] Interestingly, separate cortical regions appear to be recruited in category and letter fluency

tests which may explain a portion of the variance in results such as those of Poels and Zhong.[127,132,134,135]

2.5.4 Depression

Depression is a potential confounder which has been largely excluded in studies investigating cognitive function and hypertension.[8] The Center for Epidemiological Studies Depression Scale (CES-D) is a widely used tool to assess depression and depressive symptoms in multiple ethnicities and demographics.[136] The CES-D measures current depressive symptoms with an emphasis on depressive mood and is beneficial when examining short-term changes in depressive symptoms and during intervention studies.[137] The CES-D consists of 20 questions which are answered on a 4 point Likert scale based on frequency of symptom occurrence with cumulative scores ranging from 0-60 and scores $\geq$ 16 indicating possible clinical depression.

Recent clinical findings suggest that depressive symptoms affect responses on self-report questionnaires and are correlated with objective measures of retrospective and prospective memory.[8,136] Thus, when using self-report questionnaires and subject based assessments of cognition, it is wise to screen for presence of depression.

2.6 Pathophysiology of Hypertension Induced Cognitive Dysfunction

There are two prevailing theories on the mechanisms underlying reduced cognitive function in hypertensive individuals; 1) hypertension may exert direct effects on the brain, or 2) systemic arterial stiffening may affect brain white matter and microvasculature.[12] Current evidence favours the latter. In addition to increased central arterial stiffness (i.e. cfPWV), hypertension induces increased cerebral vascular wall stiffness and thickness,

resulting in hypoperfusion and cerebral vasoconstriction.[10,138,139] Hypoperfusion in hypertensive adults may be a contributing factor towards cognitive deficits resulting from impaired neurotransmission.[140] In fact, dissociations in blood flow to cortical regions often result in lesions to regions of high white and grey matter density such as the corpus callosum.[10] Furthermore, sustained high BP is associated with loss of arterioles and capillaries (rarefaction) in the brain.[10]

The above pathological adaptations in the brain occur more commonly and to a more severe extent in hypertensive individuals than normotensives.[10,13,141] These adaptations generally include increased presence of white matter hyperintensities (WMH), reduced grey matter, and brain atrophy.[10,142] In hypertension, these changes indicate accelerated brain aging and neurodegeneration which can be attributed to the complex interplay between vascular damage and functional reorganization of the brain.[10,143] Without the use of magnetic resonance imaging (MRI), the contribution of WMH and related structural damage to cognitive decline are unclear, and the effects of IHG training on progression or attenuation of WMH are unknown. However, it is important to acknowledge the probability of WMH and structural damage which may contribute towards cognitive impairment in a hypertensive population.

A critical region of information integration is the NTS.[144] Ascending from the NTS is the vagus nerve which reaches to the thalamus, paraventricular nucleus, amygdala, hippocampus, anterior cingulate cortex (ACC), and prefrontal cortex (PFC).[144] Dysfunction in the NTS may contribute towards upstream disturbances in cognitive processes.[144] Specifically, the frontal lobe, ACC, hippocampus, and parietal cortex are

affected by hypertension.[144–146] Disruptions in neural pathways and increased arterial stiffness may each play a role in attenuated cognition observed in hypertensive populations.

2.6.1 Blood Pressure and Cognition

Cross-sectional evidence indicates a negative linear association between SBP and cognition (Figure 2.4).[14] In community dwelling adults (mean age = 64 years), global cognitive performance and SBP were inversely related along the SBP spectrum.[14] Observing this association at the low end of the SBP spectrum suggests a minimal BP is required to maintain sufficient perfusion pressure to the brain and subsequently maintain cognitive function.[16] Importantly, this study used an array of cognitive assessments that tested multiple domains including memory, attention and executive function.[14] Brady et al. identified similar associations in men (mean age = 67 years) of varying BP categories and found uncontrolled hypertension produces cognitive deficits specific to category fluency and immediate recall beyond which can be attributed to the influence of age alone.[147]

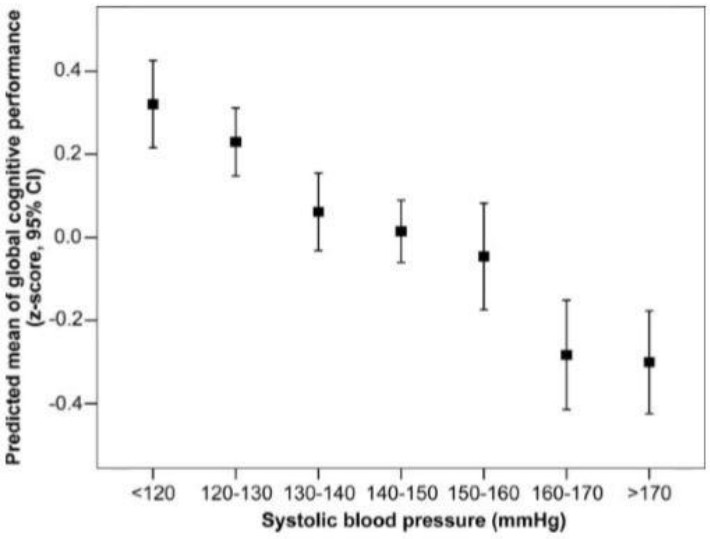


Figure 2.4 *Association of global cognitive function across a range of SBP values*. Taken from Knecht 2008.[14]

Research consistently implies an association between hypertension and cognitive impairment, although the association exists along the BP spectrum.[14,148] Many studies investigating BP and cognition are limited by their selection of cognitive assessments, namely an overreliance on a single test of cognitive function.[8] Use of cognitive test batteries assessing multiple cognitive domains is becoming more widely used in research. Hypertensive adults have been shown to experience impairments in executive function, episodic and working memory, and speed of cognition.[149] Similarly, a more recent study identified hypertension-related impairments in attention, memory, and executive function.[150] Elderly hypertensives demonstrated impaired working memory and delayed recall (long-term memory) in comparison with normotensives. In addition, close to 50% of the hypertensive adults in this sample were unable to complete the TMTB and performed a higher number of mistakes on the test than normotensives.[150] The authors concluded that effective BP management has the potential to reverse or attenuate losses in cognition associated with hypertension.

As such, studies designed to optimize hemodynamic stress and attenuate the rate of cognitive decline through effective BP management strategies among high-risk groups are needed.[16] The increasingly well-defined relation between SBP and various domains of cognition lends itself to identifying potential improvements in cognitive function following an intervention which specifically targets BP reduction. Whether IHG training is able to decrease SBP and improve cognition in hypertensive adults will be investigated in the present study.

2.6.2 Regional Arterial Stiffness and Cognition

Hypertension is considered a model of accelerated vascular aging which has been consistently associated with reduced cognitive function.[7,126,151,152] For example, in newly diagnosed, never treated hypertensive adults, an association between cfPWV and cognitive impairment was identified.[153] An independent association between cognitive function and microvascular damage was not observed in this sample suggesting a temporal association between duration of exposure to high BP and microvascular damage. In contrast, a positive association between cfPWV, extent of WMH damage and silent cerebral infarcts was present independent of age, MAP and vascular risk factors in hypertensive adults free of cardiovascular and cerebrovascular disease.[154] However, this study did not investigate severity of WMH with concurrent assessments of cognition. The continuous relationship between cfPWV and WMH suggests an absence of clear-cut thresholds. One large population-based study suggested PWV ≥12 m/s is associated with reduced cognition.[127] In a separate study, each standard deviation (SD) increase in cfPWV was associated with poorer cognitive function.[155] This association was found for global cognitive function, psychomotor speed, and perceptual speed.[155]

Extreme examples of the association between arterial stiffness and cognition are seen in populations recruited specifically for reported memory complaints and/or memory loss. Hanon et al. investigated 4 such groups based on severity of cognitive impairment: normal cognition, MCI, Alzheimer's disease, and vascular dementia.[152] Severity was significantly correlated to cfPWV (i.e. normal cognition demonstrating lowest cfPWV, vascular dementia had highest cfPWV). A reported 76% of the sample was hypertensive, while 70% of these individuals were medicated for hypertension.[152]

Longitudinal studies have primarily been interested in baseline arterial stiffness and changes in cognition. Similar to cross-sectional studies, the majority of longitudinal research to date supports the association of increased cfPWV with accelerated rates of cognitive decline in adults.[11,155,156] One of the first longitudinal studies to investigate arterial stiffness and cognition was performed in older adults with complaints of memory loss.[157] This investigation revealed cfPWV was a significant predictor of loss in cognition independent of age, sex, education and cardiovascular risk factors at an average follow-up of 12 months.[157] One longitudinal study failed to find an association between cfPWV and cognitive decline in a population based sample of adults aged 55 years and older.[132] Although cross-sectional analysis of this sample did identify small associations with stiffness and cognition, most specifically executive function.[132] The majority of large population based studies conclude that the greatest cognitive declines are often observed in individuals with highest baseline stiffness.[11,132,158]

Thus, cross-sectional and longitudinal research supports associations between increased cfPWV and reduced performance on common assessments of cognitive function. Considering hypertension is widely regarded for accelerating the progression of cfPWV, it is anticipated that the association of cfPWV with cognitive function will likewise be accelerated in hypertensive individuals. Lowering BP through IHG exercise training may provide one method by which the cfPWV and cognitive function association can be attenuated or even improved.

2.6.3 Common Carotid Artery Distensibility and Cognition

Measuring CCA distensibility in hypertensives is warranted when investigating changes in cognitive function as it may provide further information on pathways which contribute

towards functional impairment and structural adaptations. Less distensible arteries in hypertensives are associated with cerebral hypoperfusion and reduced oxygen delivery to the brain.[159] Hypoperfusion in elderly adults whom underwent aggressive BP reduction, has been shown to result in syncope, falls and declines in cognitive function.[160] Successful, long-term anti-hypertensive treatment has been shown to improve CCA distensibility, which correlated with concomitant changes in cerebral blood flow.[139,161] Therefore, improvements in CCA distensibility from a BP lowering intervention (primarily ACE inhibitors) appear to be mirrored by similar improvements in cerebral perfusion. Taken together, assessment of CCA distensibility should be sufficient to comment on changes in perfusion short of directly measuring blood flow velocity following BP reduction.

Few studies have explored CCA distensibility and cognition. One study comparing sedentary and endurance-trained older adults found that when CCA distensibility was controlled for, between-group differences in cognition were abolished.[126] In contrast, CCA distensibility was not predictive of cognitive decline or dementia within the Rotterdam study, a prospective population-based cohort study of adults older than 55 years.[132] However, those who attended the follow-up sessions were younger and of better cardiovascular health than those whom did not follow up, thus selective attrition bias may have confounded the results. Thus, changes in CCA distensibility may result in improvements in blood flow and regulation of the forward pressure wave into the brain microvasculature, with the potential for modest functional improvements in cognitive performance.

2.6.4 Autonomic Function and Cognition

Research into autonomic function and cognition is largely unexplored, however the neural pathways common to autonomic regulation of HR and BP, and cognition, stem from the NTS.[144] Dysfunctions in the NTS may compromise efferent activity to the vagus nerve and promote pathological higher order CNS activity, thus resulting in compromised neurocognitive activity.[144] Furthermore, lesions to the NTS have been shown to attenuate central baroreceptor pathways.[162] Evidence is emerging that this relationship may in fact be bidirectional, such that autonomic dysfunction progresses to cognitive impairment via systemic hypotension, or neurodegenerative processes influence autonomic pathways and thus resulting in autonomic dysfunction.[163–165] As such, the relationship between autonomic function (i.e. HRV and cvBRS) and cognitive functioning is complex and warrants further investigation.

Regarding indices of autonomic function, researchers have focused on HRV and cvBRS as a means to explore associations between detriments in cognition and autonomic function. The Irish Longitudinal Study was the first to observe attenuated HRV in individuals with low scores on the MoCA, a representative test of global cognition which tests six specific domains.[165] Researchers identified low scores in two domains; verbal recall, and language.[165] Importantly, this study was the first to identify an association between HRV and global cognition at a population level, although others have reported associations between HRV and verbal recall.[165,166] One study which evaluated the predictive ability of cvBRS on cognitive function in a healthy elderly sample of community dwelling adults, found cvBRS to be positively associated with attention and memory.[145] Furthermore, using both compound and z-scores, cvBRS was a predictor of memory z-

score. In particular, individuals with cvBRS 3-6 ms/mmHg displayed a 1.82 greater risk of developing cognitive impairment in the memory domain.[145] These findings reinforce those of the Irish Longitudinal Study listed above, which identified lower HRV quintiles were associated with lower MoCA scores.[165]

The hypothesis that neural pathways between the brainstem region and cortical areas are involved in cognitive processes needs to be further explored.[145] As indicated above, pathways involved in autonomic regulation of RRI and BP may be affected by disrupted signalling in the NTS, also resulting in reductions in cognitive functioning.[144] Whether an intervention which targets BP reduction can improve both autonomic and cognitive function has yet to be investigated. As higher cvBRS is generally observed in healthy populations, it is speculated that BP reduction can improve cvBRS and result in secondary improvements in cognition, especially within the memory domain.[145]

2.7 Intervention Studies

Exercise is associated with attenuated loss of cognition and enhanced brain health in a variety of populations.[167] Aerobic exercise in particular has been shown to improve neural and non-neural regulation of BP and result in beneficial effects on brain structure and cognitive function.[168] In agreement, aerobic exercise training results in improvements in cognitive function by both BP dependent and independent pathways.[167] Although the benefits of aerobic training on cardiovascular and cognitive health are clear, the effects of different exercise modalities on cognition are less well understood.

Chronic aerobic exercise is shown to result in lower central arterial stiffness, increased regional cerebral perfusion, and higher cognitive function when compared with

sedentary age-matched controls.[126] Collectively, these changes in cardiovascular health induced by aerobic exercise result in improvements in cerebrovascular /cognitive health which in turn may result in the greater cognitive function often observed in aerobically trained individuals. As such, the majority of evidence to date suggests that chronic aerobic exercise positively influences cognitive health.

When aerobic exercise is used over a 4-month period in addition to a combination of caloric restriction and dietary approaches to stop hypertension, improvements in neurocognitive function have also been observed.[169] Change in SBP was a significant moderator of the effects of diet and exercise on neurocognitive function in overweight/obese individuals.[169] Although the participants in this study were classified as pre-hypertensive or hypertensive, none of the participants were medicated, thus limiting the applicability of these findings to the general hypertensive population. Furthermore, this study employed a drastic lifestyle change which may not be easily integrated into everyday life. Thus, there may be a need for an intervention which can be easily adapted into daily life, have a high compliance rate, and similar effects on cognitive function.

In conclusion, several studies have been able to successfully identify improvements in cognitive function and related factors such as cerebral blood flow following an intervention which results in reduced BP. This has been shown in studies which employed dietary, pharmacological and exercise based interventions.[161,168,169] Regarding exercise studies and cognitive health, there is considerable need to examine how modalities other than aerobic exercise can influence cognitive health, specifically in a hypertensive population. A recent review on exercise, brain health, and hypertension concluded that studies utilizing exercise modalities other than aerobic training need to be investigated to

develop a more complete understanding of the relationship between hypertension and cognition; specifically citing IHG exercise as one such exercise modality.[167] This is in alignment with the purpose of the present thesis.

2.8 Objectives

This study aimed to investigate several objectives surrounding cardiovascular and cognitive health in hypertensive adults:

1. To determine the effects of 8-weeks of IHG training on markers of arterial stiffness and function (i.e. CCA distensibility, ctPWV, crPWV), in comparison to a non-exercising control (CON) group.
2. To determine the effects of 8-weeks of IHG training on autonomic function (e.g. cvBRS, HRV) in comparison to CON.
3. To examine adaptations in cognitive function following 8-weeks of IHG training in comparison to CON group.

2.9 Hypotheses

It was hypothesized that:

1. IHG training would improve local arterial stiffness and structure in the CCA. Specifically, IHG training would decrease resting BP, and the changes in systemic (i.e. ctPWV) and upper-limb (crPWV) arterial stiffness would be significantly different between IHG and control (CON) groups over the 8-week intervention, indicating that IHG training would reduce regional arterial stiffness. Additionally, that the changes in CCA distensibility and diameters would be significantly different between study groups over the 8-week intervention.

2. IHG training would result in a significant change in cvBRS in the IHG group compared with the CON group. Furthermore, HRV change would be significant in the IHG but not CON group.
3. IHG training would result in significant improvement in measure of cognitive function in the IHG group compared with the CON group.

3 Chapter 3 - Methodology

3.1 Study Design and Sample

This study received approval from the Brock University Biosciences Research Ethics Board (BREB, #15-065), and was conducted on adults in the Niagara region whom were medicated for hypertension. A repeated measures study design was utilized which involved a training group (IHG) and a control group (CON). Due to time considerations, the first eight individuals were allocated into the IHG group and the remaining individuals who contacted researchers regarding the study were placed into the CON group.

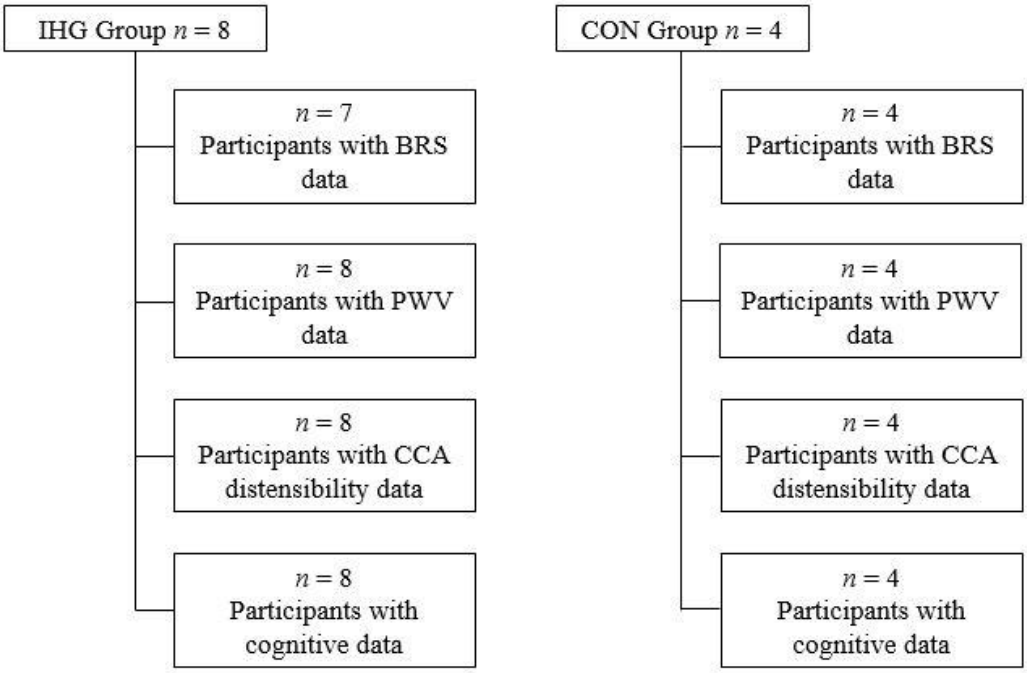


Figure 3.1 *Overview of sample sizes by arterial mechanical properties and cognitive data*.

3.2 Recruitment Protocol

Hypertensive adults were recruited from the Niagara region through a poster and email campaign and the cooperation of several local physicians. Individuals who expressed

interest in participation contacted the researchers to schedule an initial BP assessment and explanation of the study requirements.

Initial eligibility criterion required the participant to be medicated for hypertension, while the exclusion criteria consisted of hospitalization within the last three months, undergoing a medication change within the last two months, and a physical limitation which prevented proper performance of the IHG exercise. Visit 1 consisted of a complete explanation of the procedures which participants were expected to follow as part of the IHG or CON group in addition with expectations of laboratory based procedures as outlined in the Information Letter (Appendix A). If individuals were still interested in participating, they were asked to read and sign the Informed Consent form (Appendix B). A brief Medical, Physical Activity and Educational History questionnaire was then administered to each participant (Appendix C). Education was scored on a 4-point scale consisting of secondary-school education, college/2-year degree, bachelor's degree, or graduate degree. Additionally, all women responded to a question on menopause status and whether they currently or have ever used hormone replacement therapy. Following this, resting BP and HR were measured and recorded using an automated brachial oscillometric device (Omron Healthcare, HEM-780CANN, Illinois, USA). Seated resting BP and HR were measured four times, separated by two-minutes, and the final three measurements were averaged.[115] A second visit was then scheduled.

Visit 2 consisted of resting BP and HR measurement identical to that conducted at Visit 1. The average resting BP of Visits 1 and 2 was then calculated. The study investigator then conducted the MoCA, COWAT, TMT-A and TMT-B testing protocols. Participants then completed a familiarization session for the IHG exercise protocol to habituate them to

the exercise protocol. Following the above procedures, participants were provided with a copy of a physical activity readiness questionnaire (PARmed-X) and Health Care Provider (HCP) form which were to be returned and signed by their regular physician before their first testing session. The signed HCP form was the final step in the recruitment process, signifying physician approval and acknowledgement of their participation in the study. If all of the above requirements were met, subjects scheduled their first laboratory testing session with the researchers.

3.3 Outline of Experimental Measurements

Following the above protocols for study eligibility and HCP approval, participants reported to the Human Hemodynamics Laboratory (Welch Hall, room 22) where non-invasive assessments of cardiovascular health took place. Each participant was instructed to follow their standard medication regiment on all laboratory testing days and for the full study duration. Participants were instructed to avoid strenuous physical activity for the 24 hours prior to the start of testing, refrain from eating for four hours leading up to the start of testing, and to not drink caffeine or exercise on the day of testing.[30]

On the day of laboratory testing, participants were asked to void their bladder before being outfitted with laboratory equipment as a distended bladder has been shown to increase BP.[170] Anthropometric data was collected as standing height (m) and body mass (kg). Participants rested supine on a bed in a dimly lit room and were outfitted with a standard single-lead electrocardiogram for beat-by-beat collection of RRI. Additionally, a finger cuff was placed on the left middle phalange to collect beat-by-beat BP as well as a pulse oximeter on the left second toe. During this time, three manual BP readings were taken via the auscultation method by the researchers on the right upper arm. Beat-by-beat

data collection of RRI and BP was continuous throughout the laboratory session. Following a period of 10-minutes of continuous RRI and BP data collection, carotid ultrasonography was performed on the right CCA for a series of three five beat cycles.[171] Local PP was taken on the right CCA using applanation tonometry for a minimum of 15 beats. All of the experimental measures and cognitive assessments were conducted pre and post 8-weeks of IHG training and analyzed by the same researcher to minimize inter-observer variability within and between participants.

3.3.1 Cognitive Assessments

3.3.1.1 Montreal Cognitive Assessment

The MoCA (Appendix D) evaluates several cognitive domains such as executive function, attention, concentration, orientation, visuoconstructional skills, conceptual thinking, language, and verbal and visuospatial memory.[122] The suggested normal range of scores falls between 27-30 points on a 30 point scale; scores $\leq$26 are indicative of MCI.[122] Importantly, the MoCA has been demonstrated to be a more sensitive tool than the MMSE for the detection of MCI in less severe cases.[122,172] The MoCA was used in the present study to identify MCI and classify global cognition at baseline only.

3.3.1.2 Trail Making Test Parts A and B

The TMT-A (Appendix E) and TMT-B (Appendix F) are commonly used to assess multiple cognitive domains including visual search, scanning, speed of processing, mental flexibility and executive function.[173] TMT-A involves drawing a line which connects consecutive numbers from 1-25 whereas TMT-B involves drawing a similar line which alternates connecting numbers (1-13) and letters (A-L) in ascending order. Alternate versions of the tests have been developed in order to help control for early rapid

improvements observed in test-retest scenarios.[174,175] The present study utilized these alternate test versions for pre and post-training for all participants. The difference in time between TMT-B and TMT-A (TMT-BA) and ratio of TMT-B to TMT-A (TMT-B/A) were used in addition to individual test scores; the TMT-B/A was used as an index of executive function, as suggested by Arbuthnott and Frank.[125]

3.3.1.3 Controlled Oral Word Association Task

The COWAT is a letter fluency test which requires individuals to produce as many novel words beginning with the same letter as possible within three 60 second trials. Accepted forms of the COWAT include three possible letter combinations: FAS, CFL, and PRW.[176] However, the FAS version is believed to be of lower difficulty compared to the CFL and PRW versions, thus making it unsuitable for pre- post- comparisons.[177] Standard clinical practice for use of the COWAT utilizes the CFL in initial testing with PRW used in follow-up tests.[129] The present study was conducted according to these standards with the CFL trial being conducted at pre-training and PRW trial being conducted at post-training.

3.3.1.4 Center for Epidemiological Studies Depression Scale

The CES-D (Appendix G) measures current depressive symptoms with an emphasis on depressive mood and is beneficial when examining short-term changes in depressive symptoms such as intervention studies.[137] The CES-D is used to assess depression and depressive symptoms in multiple ethnicities and demographics.[136] The CES-D contains 20 questions which are answered on a four point Likert scale based on frequency of symptom occurrence within the past week. Cumulative scores range from 0-60 with scores $\geq$16 indicating presence of depression.[137]

3.3.2 Anthropometry

Participants were assessed without shoes while wearing light clothing. Height (m) was measured using a wall mounted stadiometer (STAT 7X, Ellard Instrumentation Ltd., Monroe, WA, USA) and body mass (kg) using a calibrated electronic medical scale (BWB-800S, Tanita Digital Scale, Tokyo, Japan). Body mass index (BMI) was calculated by dividing body mass by height squared (kg/m^2). Waist circumference (cm) was taken around the narrowest point and hip circumference (cm) at the greatest gluteal protuberance.[178] Each of the circumference measures were taken in duplicate to ensure accuracy.

3.3.3 Cardiovascular Measurements

3.3.3.1 Blood Pressure and Heart Rate

Resting seated BP and HR were measured and recorded using an automated brachial oscillometric device (Omron Healthcare, HEM-780CANN, Illinois, USA). Seated resting BP and HR were measured four times, separated by two-minutes, and the final three measurements were averaged.[115]

Resting supine beat-by-beat BP and RRI was noninvasively assessed throughout all laboratory based testing. Beat-by-beat BP was measured using a photoplethysmograph cuff (Nexfin, BMEYE,Amsterdam, Netherlands) attached to the left middle finger to collect measures of SBP and DBP. RRI was recorded using a standard single lead electrocardiogram. Both BP and RRI were sampled at 1000 Hz, thus providing a basic resolution of 1 ms, which is considered an optimal digitization rate.[179]

As well, three manual BP readings were taken on the right arm using a standard mercury sphygmomanometer while resting in the supine position, as is standard practice in

the Human Hemodynamics Laboratory.[180] Averages of the last two BP measures represented a resting supine brachial artery BP. The BP average was used to adjust the beat-by-beat BP values obtained at the finger using the Nexfin.

3.3.3.2 Common Carotid Artery Distensibility and Intima-Media Thickness

Following beat-by-beat data collection, resting arterial diameters were measured at the CCA. A minimum of three non-invasive imaging sequences consisting of five beat-by-beat diameter changes in the right CCA were recorded using Echo-Doppler ultrasound (Vivid q, General Electric Medical Systems, Netherlands) from a location approximately 1-2 cm proximal to the carotid bulb. CCA pulse pressures were taken non-invasively using applanation tonometry (Millar Instruments, Texas, USA) and a consistent 15 beat average was taken.[171] Ultrasound images were stored in Digital Imaging and Communications in Medicine (DICOM) format for offline analysis. Two of the best quality images were used for determining diameter measurements in systole and diastole. End-diastolic frames were determined at the time of the R-spike of the ECG recording and end-systolic frames were determined at the time of the T-wave of the ECG recording. Three cardiac cycles for each of the two images were chosen; therefore six total images were examined. These images were stacked in a new DICOM file using commercially available software (Sante DICOM Editor, V. 3.1.24; Santesoft, Athens, Greece). Images were then analyzed using a semi-automated edge-tracking software (Artery Measurement System II, Image and Data Analysis; Gothenberg, Sweden) in a specified region of interest. IMT was measured at end-diastole at the far wall for the same cardiac cycles as the vessel diameters. Pulsatile cross sectional area (CSA; m^2, where r = radius), and the corresponding CCA pulsatile pressure were used to determine vessel distensibility using the standard equation:

$$Dist\ (mmHg^{-1}) = \Delta CSA/(PP * CSAmin)$$

3.3.3.3 Pulse Wave Velocity

Pressure waveforms were recorded for a minimum of 15 cardiac cycles at the left CCA, radial and femoral arteries.[171,181] Pulse wave contours were taken using a hand-held applanation tonometer (Millar Instruments, Texas, USA) which incorporates a high-fidelity strain gauge micro-manometer on the flattened end of a pencil-type probe. This probe was positioned against the artery (i.e. CCA, radial and femoral arteries) to permit accurate registration of arterial pressure waves. Ideal conditions for applanation tonometry involve a flattening of the wall of an artery by the sensor which eliminates tangential pressures.[182] A pulse oximeter (Nellcor N-200 Tyco Healthcare Group LP, Pleasanton, CA, USA) was placed on the left second toe to similarly acquire a pulse wave contour.

The foot of each pressure waveform was identified using a bandpass filter (5-30 Hz) as has been previously used in assessments of PWV.[183] PWTT was then calculated relative to the R-wave of the ECG signal. The direct distances from the sternal notch to the carotid artery, femoral artery, and radial artery were measured using an inelastic tape held over the body. The difference between distal arterial distance (*Dd*) and proximal arterial distance (*Dp*) were then divided by the difference in PWTT of the distal (*Td*) and proximal (*Tp*) waveforms. PWV was then calculated using the subtraction method as:[58]

$$PWV = (Dd - Dp)/(Td - Tp).$$

3.4 Isometric Handgrip Exercise Training Protocol

Participants took part in an 8-week IHG training protocol. The protocol consisted of training three times a week. At each session the participants would perform two maximal

contractions (one per hand) at the beginning. From these contractions each participants 30% MVC was determined. Each participant then completed four sets of two minute 30% MVC IHG contractions separated by a one-minute rest period (Figure 3.2). Participants alternated the limb performing contractions. Two of the three weekly training sessions were monitored by the researchers at the Human Hemodynamics Laboratory at Brock University or the Brock-Niagara Centre for Health and Well-Being; the third session was unsupervised after participants were provided with a detailed description of how to properly conduct the session alone. No adverse events were reported in response to the IHG training in our sample and participants demonstrated 100% adherence to the IHG training program.

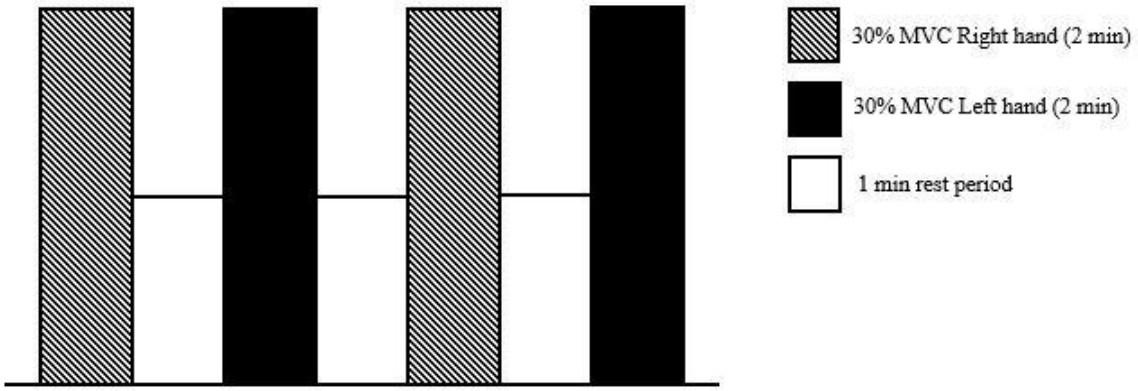


Figure 3.2 *Isometric handgrip exercise training protocol.*

3.5 Data Analysis

Calculations of BMI, WHR, CCA distensibility and diameters, and crPWV and ctPWV were made following data collection according to standardized equations (see above). Average RRI was calculated using the average time (ms) from R-wave to R-wave within a stable 1-minute period during the data collection.

3.5.1 Cardiovagal Baroreflex Sensitivity and Heart Rate Variability

Beat-by-beat RRI and BP data was collected at 1000 Hz on Powerlab and Chart 7 PRO, ADInstruments and transferred into excel (Microsoft, 2010). The cleanest, most stable 5-minutes of data was used for BcvRS analysis. The R-R sequences were visually inspected, and if any data was considered artifactual, it was manually replaced with interpolated data to ensure linear extrapolation in the time domain. Using Matlab (MathWorks 2013b), suitable series of RRI and SBP were subjected to FFT analysis for HRV (LF:0.04-0.15 Hz and HF:0.15-0.5 Hz), and transfer function analysis in of the LF domain for the calculation of cvBRS.[75,184] cvBRS gain relationships were only accepted when the coherence was $\geq$0.5.[185,186]

3.6 Statistical Analysis

Descriptive analysis are presented as mean ± SD for physical (sex, age, height, body mass, BMI, and waist and hip circumference), cardiovascular, and cognitive variables. The Shapiro-Wilk test of normality was used to determine whether data were normally distributed. Baseline between group differences were assessed by Fisher's exact test for categorical variables and independent samples t-tests for continuous variables. For training effects, pre- and post IHG training difference scores were calculated for IHG and CON groups for all variables and compared using independent samples t-tests. All statistical analyses and sample size calculations were performed using SAS (v9.4, SAS Institute, Cary, NC). Graphs were created using SigmaPlot (v11.0, Systat Software Inc., Chicago, IL).

4 Chapter 4 – Results

4.1 Descriptive Statistics

Twelve hypertensive adults participated in this study. Table 4-1 displays the subject demographic, anthropometric, and hemodynamic data stratified by group. Data are presented as group means and by intervention group (IHG vs CON). No significant differences were identified between IHG and CON groups for demographic and hemodynamic variables ($p>0.05$; all). Although not statistically significant ($p=0.096$), members of the CON group (70 ± 5.7 years) were slightly older than were those of the IHG group (61 ± 9.6 years). Moreover, there were no significant differences between groups for education levels or medication usage ($p>0.05$; all).

Table 4.1 *Subject demographics, anthropometrics, and education history*

	Group (n = 12)	IHG (n = 8)	CON (n = 4)	p
Female, *n (%)*	5 (42)	3 (37)	2 (50)	1.000
Age, *yrs*	64 ± 9.5	61 ± 9.6	70 ± 5.7	0.096
Height, *m*	1.68 ±0.10	1.69 ± 0.12	1.66 ± 0.05	0.573
Body mass, *kg*	83.1 ± 14.7	87.4 ± 16.5	74.4 ± 3.6	0.158
BMI, kg/m^2	29.3 ± 3.56	30.3 ± 3.54	27.1 ± 2.91	0.160
WHR	0.95 ± 0.06	0.95 ± 0.07	0.96 ± 0.06	0.833
SBP, *mmHg*	132 ± 9	132 ± 11	133 ± 9	0.869
DBP, *mmHg*	81 ± 10	85 ± 9	76 ± 8	0.134
PP, *mmHg*	51 ± 10	47 ± 9	57 ± 13	0.155
Education level		%		
High-school	42	37.5	50	0.576
College	0	0	0	1.000
University	25	25	25	0.764
Post-graduate	33	37.5	25	0.594
Medications		%		
ACE inhibitor	42	50	25	0.424
Diuretic	42	50	25	0.594
β-Blocker	58	63	50	0.576
Ca^{+2} Channel Blocker	25	25	25	1.000
Angiotensin receptor blocker	8	0	25	0.764
α-2 receptor agonist	8	13	0	0.667
α-1 receptor agonist	8	13	0	0.667
Vasodilators	8	13	0	0.667
Statin	58	75	25	0.152
Aspirin	58	50	75	0.594

Values are means ± SD. Independent samples t-tests were used on all continuous variables and Fisher's exact tests were used on categorical variables.
BMI, Body mass index; WHR, Waist-to-hip ratio; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; PP, Brachial pulse pressure.

4.2 Baseline Cardiovascular and Cognitive Characteristics

Baseline between group differences in cardiovascular (Table 4.2) and cognitive (Table 4.3) variables were assessed. One participant from the IHG group was removed from autonomic analysis as an outlier and one from ctPWV due to equipment malfunctioning. No statistically significant differences were identified for any cardiovascular or cognitive variable ($p>0.05$; all).

Table 4.2 *Baseline Cardiovascular characteristics*

	n	IHG	n	CON	p
Dd, *cm*	8	6.92 ± 0.60	4	7.51 ± 1.27	0.292
Ds, *cm*	8	7.32 ± 0.57	4	7.77 ± 1.47	0.588
CCA PP, *mmHg*	8	22.5 ± 6.3	4	20.5 ± 6.1	0.609
Distensibility, $mmHg^{-1} \times 10^{-3}$	8	5.55 ± 1.97	4	3.07 ± 1.94	0.066
IMT, *mm*	8	0.426 ± 0.145	4	0.547 ± 0.096	0.167
crPWV, *m/s*	8	8.91 ± 1.19	4	8.26 ± 1.58	0.445
ctPWV, *m/s*	7	6.99 ± 0.62	4	6.54 ± 0.30	0.207
cvBRS, *ms/mmHg*	7	6.23 ± 2.59	4	9.12 ± 3.29	0.140
LF HRV	7	330 ± 278	4	833 ± 961	0.376
HF HRV	7	149 ± 99	4	844 ± 1404	0.395
LF/HF	7	2.05 ± 0.708	4	2.17 ± 1.10	0.822

Values are means (±SD). Independent samples t-tests were used. Dd, Diastolic diameter; Ds, Systolic diameter; IMT, Intima media thickness; PP, CCA pulse pressure; cvBRS, Cardiovagal baroreflex sensitivity; LF-HRV, Low-frequency heart rate variability; HF-HRV, High-frequency heart rate variability; LF/HF, Ratio of low to high-frequency heart rate variability; ctPWV, Carotid-toe pulse wave velocity; crPWV, Carotid-radial pulse wave velocity.

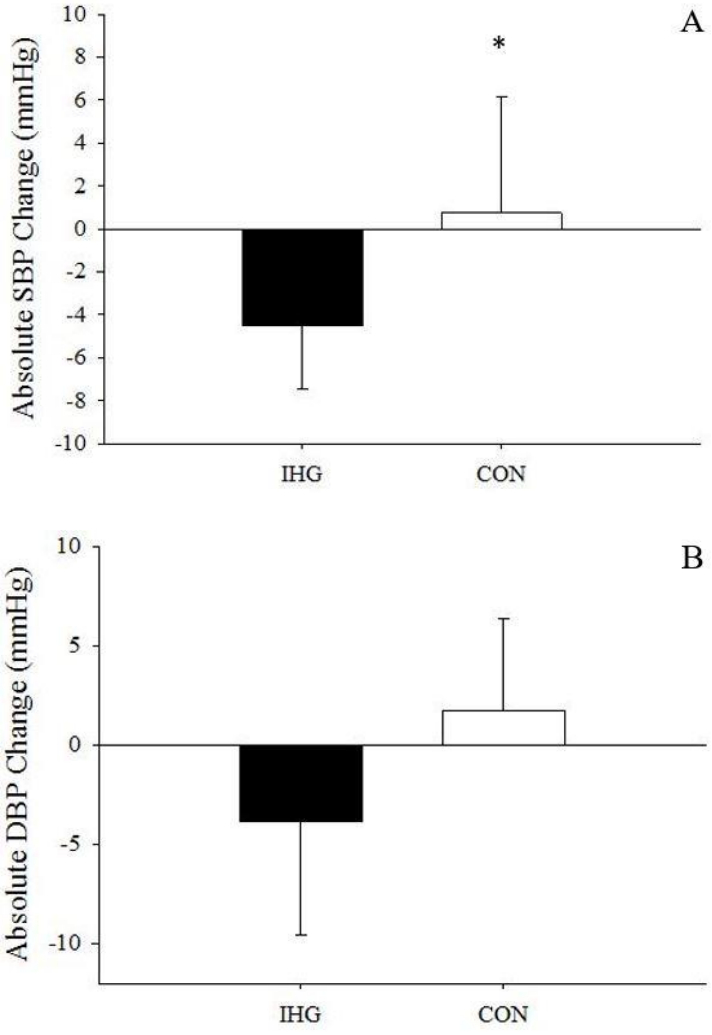
Table 4.3 *Baseline Cognitive Characteristics*

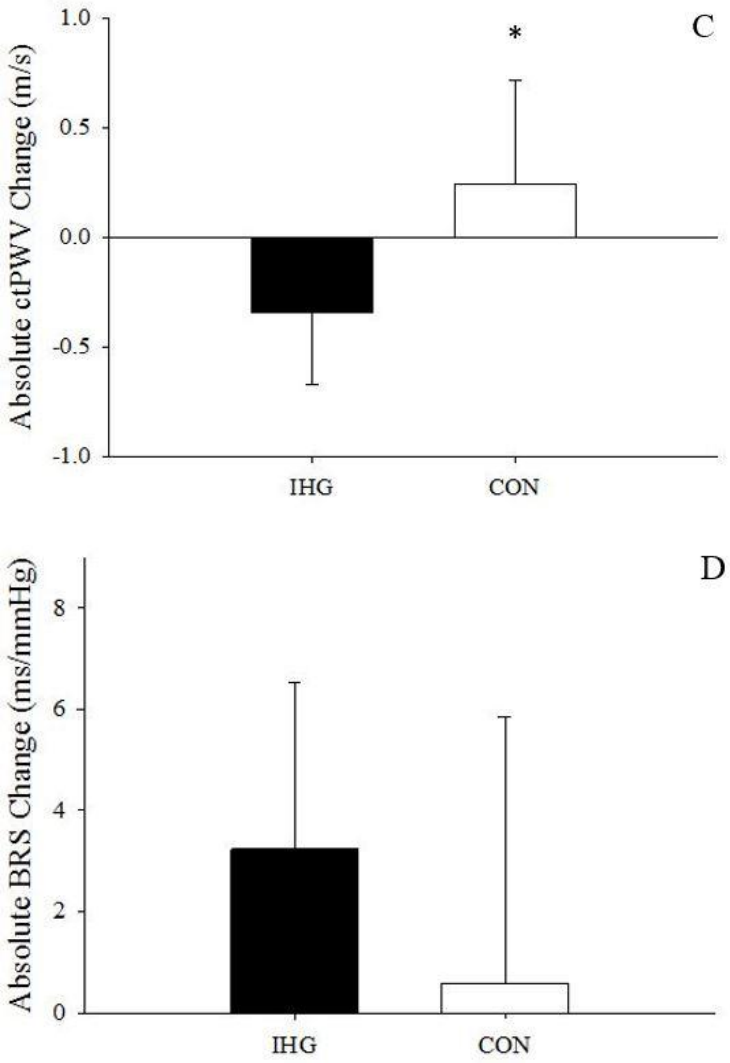
	n	IHG	n	CON	p
TMT-A, *sec*	8	25.9 ± 6.9	4	23.3 ± 6.7	0.547
TMT-B, *sec*	8	65.8 ± 34.5	4	74.34 ± 32.7	0.690
TMT-BA, *sec*	8	39.8 ± 28.9	4	51.04 ± 31.4	0.553
TMT-B/A	8	2.4 ± 0.80	4	3.3 ± 1.6	0.342
COWAT, total	8	43.7 ± 9.5	4	43.75 ± 20.0	1.00

Values are means (±SD). Independent samples t-tests were used. TMT-A, Trail-making test part A; TMT-B, Trail-making test part B; TMT-BA, Trail-making test B minus A; TMT-B/A, Ratio of TMT-B divided by TMT-A, COWAT, Controlled oral word association task.

4.3 Cardiovascular Responses to IHG Training

Figures 4.1 A-D show that the absolute changes in SBP, DBP, ctPWV, and BRS. SBP and ctPWV were significantly reduced in the IHG group in comparison to the CON group ($p<0.05$, all). Table 4.2 provides a complete summary of the change in all cardiovascular variables including SBP, DBP, and PP between IHG and CON groups from pre- to post-testing sessions. Although not statistically significant, the IHG group demonstrated an increase in cvBRS (3.24 ± 3.30) compared to the CON group (0.59 ± 5.25), which equated to an ~53% increase from baseline.





Figures 4.1 A-D. Effects of 8 weeks of IHG training on (A) SBP, (B) DBP, (C) ctPWV, and (D) cvBRS. Independent samples t-tests were employed to test the difference in absolute change between IHG and CON groups. Bars represent group means and error bars represent SD.
*indicates $p<0.05$.

Table 4.4 *Cardiovascular changes following IHG training and control periods*

	IHG	CON	p
ΔSBP, *mmHg*	-4.5 ± 2.9	0.8 ± 5.4	0.049
ΔDBP, *mmHg*	-3.9 ± 5.7	1.8 ± 4.6	0.120
ΔPP, *mmHg*	-0.63 ± 5.60	-1.00 ± 6.48	0.919
ΔDd, *cm*	-0.01 ± 0.04	-0.01 ± 0.03	0.511
ΔDs, *cm*	-0.01 ± 0.05	0.01 ± 0.03	0.952
ΔCCA PP, *mmHg*	-1.9 ± 6.9	2.8 ± 3.3	0.237
ΔIMT, *mm*	0.27 ± 0.42	-0.17 ± 0.31	0.089
ΔDistensibility, $mmHg^{-1}$ *x* 10^{-3}	0.26 ± 0.77	1.34 ± 2.03	0.203
ΔctPWV, *m/s*	-0.34 ± 0.33	0.24 ± 0.47	0.040
ΔcrPWV, *m/s*	-0.48 ± 1.26	0.11 ± 1.11	0.446
ΔcvBRS, *ms/mmHg*	3.24 ± 3.30	0.59 ± 5.25	0.325
ΔLF-HRV	588 ± 680	1073 ± 2060	0.676
ΔHF-HRV	240 ± 341	-280 ± 1490	0.382
ΔLF/HF	1.05 ± 1.60	1.77 ± 1.10	0.447

Values mean ± SD. Independent samples t-tests were used on all change variables. Dd, Diastolic diameter; Ds, Systolic diameter; IMT, Intima media thickness; PP, pulse pressure; ctPWV, Carotid-toe pulse wave velocity; crPWV, Carotid-radial pulse wave velocity; cvBRS, Cardiovagal baroreflex sensitivity; LF-HRV, Low-frequency heart rate variability; HF-HRV, High-frequency heart rate variability; LF/HF, Ratio of low to high-frequency heart rate variability.

4.4 Cognitive Responses to IHG Training

Figure 4.2 represents the absolute change in TMT-A score for the IHG and CON groups. A significant ($p<0.001$) decrease in TMT-A score was identified with the IHG group demonstrating a 3.65 ± 3.40 second reduction in time to completion when compared against the CON group. Furthermore, Table 4.3 provides a summary of the remaining cognitive outcome variables collected in this study. Both groups demonstrated non-significant reductions in TMT-B, TMT-BA, TMT-B/A (all $p>0.05$); indicating that IHG training had no effect on these assessments of cognitive function.

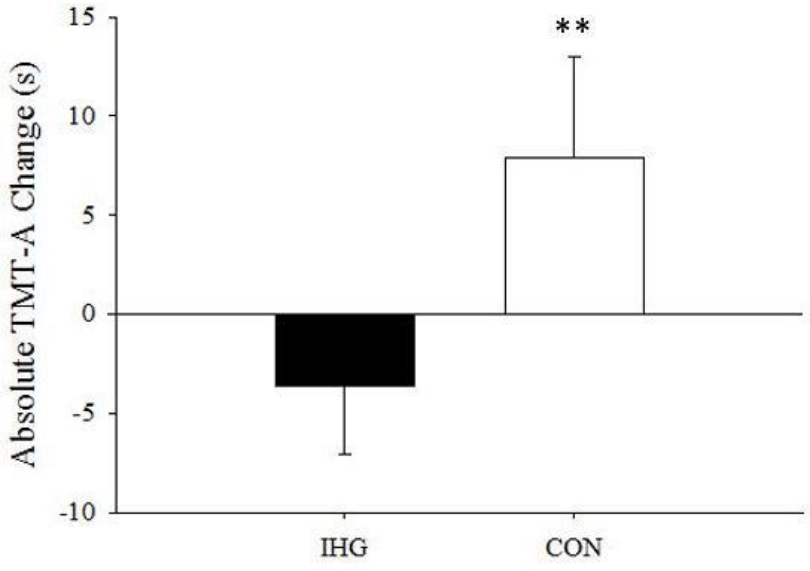


Figure 4.2. Effects of 8 weeks of IHG training on Trail Making Test Part A (TMT-A) score. Independent samples t-tests were employed to test the difference in absolute change between IHG and CON groups. Bars represent group means and error bars represent SD.
**indicates $p<0.001$

Table 4.5 *Cognitive adaptations following IHG training and control periods*

	IHG	CON	p
ΔTMT-A, *sec*	-3.6 ± 3.4	7.92 ± 5.0	<0.001
ΔTMT-B, *sec*	-18.9 ± 25.2	-12.2 ± 15.1	0.640
ΔTMT-BA, *sec*	-15.2 ± 25.1	-20.1 ± 17.9	0.737
ΔTMT-B/A	-0.27 ± 0.88	-1.37 ± 1.28	0.109
ΔCOWAT, *total*	-1.2 ± 6.2	0 ± 3.5	0.72
ΔCES-D, *score*	0.75 ± 1.49	-0.50 ± 1.29	0.184

Values mean ± SD. Independent samples t-test employed. TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; TMT-AB, Trail Making Test Part B minus Part A; TMT-B/A, Trail Making Test Part B divided by Part A; COWAT, Controlled Oral Word Association Task; CES-D, Centre for Epidemiological Studies Depression Scale.

5 Chapter 5 – Discussion

5.1 Introduction

This study aimed to investigate whether 8-weeks of IHG training would have beneficial effects on measures of cardiovascular and cognitive health. These objectives were decided upon given a multitude of recent research outlined below. Although considerable evidence supports the beneficial effects of aerobic and dynamic resistance exercise on cognitive function, no study to date has examined whether isometric exercise can have a similar effect on cognitive function.[167]

There are several novel findings of the present study. This is the first study to identify a reduction in systemic arterial stiffness following IHG training as well, a trend towards increased cvBRS. Furthermore, this was the first IHG training study to examine changes in cognitive function, identifying increased motor and visual control and speed.

5.2 Cardiovascular Adaptations: Mechanisms

A significant reduction in SBP and a trend towards a reduction in DBP following 8-weeks of IHG training was observed in this study. No change in RRI (HR) was observed, in agreement with previous findings that HR is unaffected by IHG training.[95,97,109,187–189] Previously, studies have identified both reductions and no change in BP following IHG training in medicated hypertensive populations.[19,95,98,101] However, there is considerable variability in the age, health status, and degree of BP control in the participants used in these studies. Taylor et al. identified substantial reductions in SBP and DBP in their sample of hypertensive adults demonstrating poor BP control, although 75% of the sample were treated for high BP. In comparison, our sample consisted of individuals with varying

degrees of BP control, from well to poorly controlled. This range may have resulted in the lack of a significantly observed change in DBP following IHG training.

5.2.1 Regional Arterial Stiffness

We identified a significant reduction in ctPWV in the IHG group following training. This is the first study to show systemic reductions in arterial stiffness following isometric training. It has been suggested that NO may be a key regulator of arterial stiffness in several clinical populations as its absence often results in increased central PWV.[117] Previous IHG studies have mainly identified local adaptations in vascular function (i.e. increased brachial artery dilation following FMD) and have rarely examined the systemic effects of this exercise modality.[187]

HR is a known confounder of PWV.[190] As HR increases, so too does PWV such that if the same individual has a HR of 60 bpm vs 100 bpm, the average difference in cfPWV has been estimated at 1.36 ± 2.9 m/s.[190] Of importance when considering the results of our study, we did not observe a significant change in HR following IHG training, thus it is unlikely that change in HR played a significant role in the reduction of ctPWV. It is possible that various phases of the cardiac cycle may have been altered following IHG training and thus contribute towards the reduction in ctPWV observed.[191] It has previously been shown that the pre-ejection period of the cardiac cycle, not HR itself, may also confound PWV and should be investigated in greater detail, especially when examining PWV adaptations following IHG training.[191] No IHG study has examined whether pre-ejection period is affected by the training protocol.

Contrary to our initial hypothesis, we did not observe a reduction in upper-limb arterial stiffness (i.e. crPWV) with IHG training. This lack of change may be due to little or no change in sympathetic tone or catecholamine concentrations being insufficient to reduce PWV. The human ageing model shows that central arterial stiffness is more prone to increased levels of stiffness with advancing age than peripheral arterial stiffness (Figure 2.1). This is in part due to the composition of the arterial walls in central and peripheral arteries and their ability to buffer pulsatile stress. We can hypothesize that the training stimulus used in this study may not have been of sufficient duration and/or intensity to elicit adaptations in resting peripheral arterial stiffness in hypertensive adults. Furthermore, without invasively assessing the arterial composition following IHG training, we cannot comment on alterations in arterial wall composition (i.e., collagen and elastin ratio).

5.2.2 CCA Mechanical Properties

CCA mechanical properties were unchanged following IHG training. A previous study identified improvements in femoral artery diameter, blood flow velocity and vascular conductance following isometric leg training in middle aged males.[187] Similarly, following IHG training, increased brachial artery responsiveness to FMD has been identified, suggesting improved local vascular endothelium-dependent vasodilation.[17,110] However, the CCA represents a hybrid arterial phenotype not entirely characteristic of the elastic central arteries and not of equal musculature to the peripheral arteries.[49]

Lipsitz et al. have shown that aggressive anti-hypertensive therapy produces increased CCA distensibility and cerebral blood flow velocity in hypertensive adults.[161] A treatment regimen consisting of Lisinopril with or without hydroclorothiazide, or nifedipine or an ARB, if not tolerated, to reduce SBP to <140 mmHg was used for 6

months.[161] It was only in their uncontrolled hypertension group (160/84 ± 6/5 mmHg) that these changes were identified, whereas normotensive and controlled hypertensive groups exhibited no change in CCA distensibility.[161] Our findings regarding CCA distensibility are in opposition to those of Lipsitz et al. likely due to disparities in BP status of treatment groups, intervention and participant age. Furthermore, our reductions in BP were modest in comparison to those of Lipsitz et al. (17 vs 4 mmHg) in part due to our relatively well-controlled and younger sample. Thus, it remains a possibility that had the BP reduction been of a larger magnitude, we may have observed similar increases in CCA distensibility as Lipsitz et al.

5.2.3 Autonomic Function

Although we did not observe statistically significant improvements in cvBRS, the IHG training group demonstrated a ~53% increase in cvBRS. Previously, the only autonomic measure to have been assessed following IHG training was HRV and BPV, which has demonstrated mixed responsiveness.[98,99,101,189] IHG training has been shown to improve traditional and non-traditional measures of HRV in some populations of hypertensive adults, as well as having no effect in others.[97–99,101] It has been speculated this heterogeneity in autonomic response to IHG training may be due to pharmacological agents exerting a maximal effect on the threshold for autonomic improvement in medicated hypertensive populations. We demonstrated the first evidence that IHG training may have beneficial effects on cardiovagal baroreflex function. Importantly, the changes observed in this study surpassed the expected day-to-day variability of the measure (e.g. 13.5 – 35%).[192,193]

cvBRS is a clinically relevant measure of autonomic health, and low cvBRS is an independent risk factor for all-cause mortality following MI.[68] Thus, a simple and effective

method of increasing cvBRS is warranted in order to reduce risk of adverse cardiovascular events in high-risk populations. Aerobic exercise is highly regarded for its ability to improve cardiovascular health, including cvBRS, yet requires a substantial time commitment in order to achieve the desired effects.[194,195] IHG is well established at having a low-moderate acute BP response and involves a cardioprotective effect on the heart in comparison to aerobic exercise.[15] Furthermore, the ability to perform the IHG training protocol utilized in this study requires minimal supervision and is shown to be effective in physically active and inactive populations of varying ages and health status.[98,109,114] Thus, additional research should be undertaken to examine the effects of IHG training on cvBRS in other clinical populations whom may benefit from the improvements observed in cvBRS.

5.3 Cognitive Adaptations

This was the first study to investigate the influence of IHG training on cognitive function. Extensive literature indicates aerobic exercise has beneficial effects on cognitive function in many populations.[126,195] Similarly, resistance exercise is also known to result in improvements in cognitive function.[196] Isometric exercise produces similar health benefits to that of aerobic and resistance exercise, and requires a fraction of the time commitment. Thus, if isometric exercise can induce similar cognitive benefits as aerobic and resistance exercise, it may lead to potential intervention strategies which target attenuating cognitive decline or even enhancing cognitive function, especially in populations of lower fitness levels.

Significant improvements in time to completion of TMT-A in the IHG training group compared to the CON group were observed. This is indicative of increased motor

and visual control and speed, suggesting that IHG training improved this aspect of cognitive function independent of learning effects. It can be hypothesized that this adaptation was a result of several physiological interactions. The reduction in SBP and improvement in vascular health observed in our IHG group may be responsible for mediating the improvement observed in TMT-A score. Previous studies have concluded that individuals with poorer vascular health experience significant improvements in cognitive function following a period of intervention.[169]

These improvements in TMT-A score may be a result of the reduction in SBP and arterial stiffness which buffers forward pulsatile stress into the cerebral vasculature. The relationship between large artery stiffness and pulsatile stress into the microvasculature of the brain is well documented, with researchers having shown aortic stiffness is an independent predictor of small vessel disease in hypertensive patients.[154] Moreover, research to date has focussed on investigating the cross-sectional relationship between markers of large artery stiffness, cognition, and cerebral small-vessel damage, with few utilizing interventions which target reductions in arterial stiffness. Of those who have, the interventions have involved drastic lifestyle alterations, which would be difficult to maintain outside of research settings and have been of similar duration to our study (8-16 weeks).[161,169] Although, our IHG training did result in modest improvements at the recommended training frequency and duration, the adaptations observed in our study and those of others may be enhanced with a longer intervention, as a longer intervention may allow for optimal effects. Whether maintaining IHG training over a prolonged period of time (i.e. >16 weeks) would result in greater and sustainable enhancements in cognitive function remains to be determined and should be a subject of future investigations.

An alternative theory for the improved cognitive function observed in the current study may be due to changes in cerebral perfusion and the neurotransmitters glutamate and amyloid-β.[126] As the brain requires a constant supply of blood flow to maintain homeostatic cognitive processes, certain factors contribute towards achieving this outcome. The brain accounts for 2% of the body's mass but requires ~15% of CO.[197] Cerebral hypoperfusion is known to result in increased release of glutamate, the most abundant excitatory neurotransmitter in the brain, and is crucial to memory and learning functions.[198] Furthermore, cerebral hypoperfusion results in harmful levels of glutamate and amyloid-β. Both may be due to low elasticity of central arteries as well as that of the CCA.[126] As cerebral perfusion was not assessed in this study, it is unclear whether changes in CBF may have contributed towards the improvements in TMT-A score following IHG training. Nor was functional MRI assessed to determine whether local changes in CBF occurred during the task or at baseline. Thus, little is known regarding the possible reductions in glutamate and amyloid-β accumulation in the brain and how it may have influenced cognitive function in this sample.

5.4 Strengths and Limitations

The present study has several strengths. First, multiple cognitive assessments were utilized (i.e. TMT-A, TMT-B, COWAT, MoCA) instead of relying on a single assessment, thus allowing us to examine multiple indices of cognitive function.[122,175,176] Secondly, measures were taken to limit the influence of learning effects on the TMT and COWAT respectively. For example, alternative TMT-A and TMT-B trails were developed for participants' pre- and post- assessments based on previously established methods which cite no significant difference across test versions in trail length and time to completion.[175] Alternate versions

of the COWAT were also used as is standard clinical order for CFL to be followed by PRW.[177] Third, regarding cardiovascular measures, use of local arterial PP at the CCA is considered a strength as this approach enables accurate calculation of distensibility compared to using brachial PP which underestimate distensibility due to peripheral PP amplification.[48] Fourth, although time of day for testing across study participants was not controlled (i.e. exclusively morning sessions), each individual reported for all laboratory based testing sessions within 1-2 hours of their initial laboratory testing start time. Fifth, all testing and analysis were performed by the same investigator using standardized laboratory procedures for each participant, thus limiting inter-observer variability. Lastly, all individuals in this study were on medication to manage their BP and at baseline were a relatively well controlled sample.

This study does also possess several limitations. First, although not statistically different, the CON group age was greater than that of our IHG group. This may have confounded both cardiovascular and cognitive outcomes and comparisons between groups.[14,143,147,151] Participants were enrolled in the study on the basis of contact with the study investigators and not specifically to fulfill age and sex-matched criterion. Additionally, assignment into study groups was not done at random due to the continuous enrollment of participants into the study and not knowing the total number of individuals whom would enroll. Second, aerobic fitness was not assessed and thus it cannot be ruled out that some individuals may have been of greater aerobic fitness level than others which could have confounded both cardiovascular and cognitive outcomes.[126,167] However, participants were instructed to maintain consistent diet and exercise habits during the 8-weeks of the study and study investigators verbally assessed this consistency on a weekly

basis. Third, although it was an initial goal of this study to utilize cfPWV as the main measure of central arterial stiffness, we were only able to obtain valid femoral pulse wave signals via applanation tonometry on a small portion of participants (n=3) due to participant non-compliance (did not wear proper attire or did not feel comfortable with the measurement site) in order to obtain the femoral pulse. ctPWV was instead used as an index of central arterial stiffness which has been shown to closely correlate to cfPWV and displays similar test-retest variability to cfPWV.[181] Fourth, central adiposity may have resulted in increased measurement distance used in the calculation of PWV; ultimately resulting in a lower PWV value.[48] Fifth, blinding strategies were not employed in this study for either the participants or investigators. Therefore expectation bias may have influenced our results.

5.5 Future Directions

Considering the current findings, several future topics should be investigated. This study did not investigate possible changes in MSNA. It has previously been shown that MSNA is unaffected by IHG training in young adults; whether MSNA is improved in hypertensive populations following an IHG training protocol similar to that utilized in the present study has not yet been investigated.[96] It is known that hypertensive populations demonstrate increased sympathetic discharge during isometric exercise compared with normotensive populations.[107] These exaggerated sympathetic and pressor responses exist following a period of post-exercise ischemia, suggesting an overactive metabolic component of the pressor reflex in hypertensive individuals.[199] In a normotensive population, isometric endurance exercise attenuates the MSNA response to an endurance isometric contraction.[200] However the chronic exposure of forearm vasculature to by-products of

anaerobic metabolism during IHG training may augment this pressor response and result in attenuated MSNA responses to isometric exercise in hypertensive populations.[199] For this reason, in future studies, MSNA and cvBRS should be investigated concurrently in hypertensive populations.

Similarly, a study which utilizes aerobic + IHG, or resistance + IHG to compare whether IHG exerts an additive effect on cardiovascular health has not been conducted. One merit to IHG exercise is that it is simple and time-efficient to perform, thus making it a perfect adjunct therapy to aerobic or resistance exercise. High aerobic fitness is associated with higher cognitive function in addition to preservation of cognitive function over follow-up.[126,167,201] It has previously been determined that IHG is able to reduce BP in healthy individuals who participate in regular physical activity.[17,98,114,188] However, the physical activity in question was of an unknown type, duration, intensity, and frequency and VO_2 was not assessed in any study involving IHG. Thus, whether a combined aerobic + IHG or resistance + IHG training regimen can provide increased cognitive adaptations compared to each individually may be a research area to be explored in future studies.

Furthermore, future studies should consider the long-term (e.g. 12-weeks to 6 months) effects of IHG training on cognitive function. Our IHG training period was 8-weeks in duration, which may have been too short to identify noticeable effects on cognition. A 2010 study on dietary approaches to stop hypertension demonstrated in a 16-week period that participants of poorer cardiovascular health were more likely to see improvements in cognitive function following their intervention.[169] These improvements were however mediated by weight loss, increased aerobic fitness and to some extent a reduction in SBP.[169]

Thus, lengthening the intervention period and/or increasing the training intensity may result in more substantial adaptations in cognitive function following IHG training.

This was the first study, to our knowledge, to investigate the effects of IHG training on cognitive function in any population. Our study was effectively powered to detect significant change in SBP and as such, the cognitive adaptations were not factored into power calculations. Knowing the magnitude of change in cognitive variables from this study, future studies can effectively be powered to detect similar changes of these magnitudes in their samples in order to better establish the effects of IHG training on cognitive function. Secondly, although attempts were made to reduce the likelihood of learning effects in the current study and to provide alternate versions for retesting purposes, future studies may consider utilizing more sensitive cognitive tests designed to detect small changes in cognition. The TMT and COWAT were selected for this study due to their prevalence in the literature and for the availability of multiple testing forms.[175,176] Additionally, in order to draw direct comparisons between changes in the current sample and those of other studies, the TMT and COWAT were selected. For example, a commonly used test of executive function, specifically cognitive inhibition and shifting cognitive set, is the Stroop Colour-Word Task. Providing a more widely used assessment of executive function with numerous variations may allow for future research in isometric exercise training studies on cognitive function to track changes over a longer period of time and detect smaller differences.

5.6 Conclusions

This study aimed to investigate the effects of 8-weeks of IHG training on cardiovascular and cognitive health in hypertensive adults. Previous research indicates that chronic IHG exercise has beneficial effects on local vasculature in the trained limbs of medicated hypertensives but fails to exert a systemic effect on vasculature unrelated to the intervention/exercising limbs.[115,187] Researchers have consistently shown the association between high BP and cognitive decline later in life as well as lower cognitive function when compared against age-matched normotensive adults.[8,9,11,14] These same researchers suggest investigating methods designed towards improving both cardiovascular and cognitive health in these populations to attenuate both the adverse effects of hypertension. One such intervention which could achieve both adaptations is IHG training which we hypothesized would improve a number of factors associated with poor cognitive function such as BP, arterial stiffness, and BRS. The beneficial effects of aerobic and more recently resistance exercise training on cardiovascular and cognitive health are well acknowledged in research settings.[167] These studies generally find regular exercise leads to improvements in cognition as well as attenuated rates of cognitive decline.[126,169] Yet, no study has investigated whether the much less time consuming and equally effective IHG training can result in similar or greater improvements in cardiovascular and cognitive health than aerobic, resistance, and even pharmacological methods. The current study utilized an 8-week IHG exercise training study consisting of 3 days/week training, 2 days of which were supervised, in hypertensive adults. Each training session involved bilateral handgrip training held at 30% MVC for 2 minutes for a total of 4 sets separated by 1 minute, alternating hands after each contraction. All participants completed all training days and

achieved the minimum required compliance score (90%) which indicates a successful training session.

Significant reductions in SBP, ctPWV, and TMT-A score following 8-weeks of IHG training in hypertensive adults were observed. There was a failure to observe changes in CCA distensibility and diameters following training. Moreover, the expected change in crPWV was not observed, perhaps due to the predominantly muscular composition of peripheral arteries. The lack of change in CCA distensibility and diameters is in agreement with previous literature investigating the effects of isometric exercise on arterial structure and function not localized to the training limb.[187] Additionally, a 53% increase in cvBRS was observed, although it failed to reach statistical significance in our study. This is the first study to observe systemic reductions in arterial stiffness as well as improvements in cognitive function following isometric exercise training. Future research should consider the combined effects of aerobic + IHG or resistance + IHG exercise on cognitive health to determine if there is an additive effect. Additionally, future investigations should focus on the effects of long-term IHG training on PWV, cvBRS, and cognitive function as well as introduce measures such as CBF and structural alterations in the brain for a more comprehensive understanding of the potential benefits of IHG training.

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Appendix A

INFORMATION LETTER

You have been invited to take part in a research study. This letter will outline the purpose of the project, describe the procedures that are required, tell you about potential risks and benefits to yourself, and discuss your rights and confidentiality issues. If you wish to participate, you will be asked to sign a consent form at the end of this letter. Feel free to ask any questions you might have at any time.

Study Title:
Influence of Isometric Handgrip Exercise Training on Cardiovascular and Cognitive Health in Hypertension

Researchers and Contact Information:
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Garden City Family Health Team, Montebello Medical Centre, 118 Lake Street, St Catharines, ON, L2R 5Y1.

Collaborators
Cheri McGowan, PhD phone: 519-253-3000 ext. 2451 e-mail: mcgowanc@uwindsor.ca

What is the purpose of this study?
In Canada, 1 in 5 people have high blood pressure, or resting blood pressure numbers that are ≥ 140/90 mmHg. In addition, high blood pressure has been linked to lower cognition and faster rates of cognitive decline as you age.

High blood pressure is commonly associated with greater stiffness of the large arteries and a poorer ability to manage both short and long-term blood pressure. Exposure to high blood pressure over a long period of time (i.e. several years) may lead to worse cardiovascular health and potential impairments in cognitive function.

A new blood pressure management therapy, isometric (constant squeeze) handgrip exercise training lowers resting blood pressure in people with high blood pressure, and even those with well-controlled blood pressure. Squeezing a small handgrip device for 2 minutes, 4 times, 3 days per week for 8 to 10 weeks is now suggested by the American Heart Association as a way to lower blood pressure. This study will look at how this type of exercise affects your blood pressure and the stiffness of your arteries. It also aims to investigate the relationship that blood pressure has with your cognitive health and whether this can be improved as a result of the exercise training.

Am I eligible?

This study focuses on men and women diagnosed with high blood pressure who are on a consistent medical regimen.

Study Inclusion Criteria

- Currently taking medicine prescribed to lower your blood pressure

Study Exclusion Criteria

- Any hospitalization within the past 3 months
- Change in medication within 2 months or over the course of the intervention period
- Physical limitation preventing proper performance of handgrip exercise

What are the procedures? Will there be any risk involved?

Preliminary procedures:

If you volunteer to participate in this study, you will be asked to attend the following:

Visit #1 *(approximately 30 minutes):*

You will meet with the study investigators at the Brock-Niagara Centre for Health and Well-Being where you will receive information and consent forms regarding the study. At this time, one of the study investigators will explain all parts of the study, if you are still interested in participating, you will be asked to sign the consent form and fill out a brief medical questionnaire. If you are still eligible, you will then have your blood pressure measured on your upper arm, similar to how it is taken in a doctor's office. Your resting blood pressure and heart rate will be measured after 10 minutes of seated rest and repeated 4 times, with 2-minutes of rest between measures. Following the above procedures, your second visit will be scheduled.

Visit #2 *(approximately 40-50 minutes):*

If you are still interested in participating in the study, and you are initially eligible after **Visit #1**, you will meet with the investigators again. First, you will have your resting blood pressure measured in the same manner as **Visit #1**. You will then practice all parts of the study, including performing the handgrip exercise (four 2 minute squeezes, separated by 1

minute of rest, and alternating hands after each squeeze). You and the study investigators will then schedule your first laboratory testing day.

Laboratory Testing Days (approximately 2-3 hours):
All laboratory testing will take place at the same time of day, in a quiet room located at **Brock University in Welch Hall room #22**. In total, you will be required to come into the laboratory on 3 occasions throughout the study: **Week 0, Week 9, and Week 12**. Before each testing session, you will be asked to go to the washroom, as a full bladder can increase your blood pressure. All the procedures involved in the laboratory testing are listed below:

Body Measurements which include your height, weight, and waist and hip circumferences will be measured.

Heart Rate will be monitored by an electrocardiogram. Two sets of disposable, single-use electrodes will be placed just below each collar bone and on the lower left side near your ribs. There is a very small chance that you might develop a skin rash from the adhesive on the electrodes, but there is no way of knowing if you will be sensitive ahead of time. If a rash develops, the investigators can provide hypoallergenic gel.

Blood Pressure will be measured using two methods. In addition to the traditional method which involves the arm cuff and stethoscope, a small cuff will be wrapped around the middle finger on your left hand. This cuff will apply a light pressure around the finger, which allows us to measure the blood pressure for each heart beat throughout the study. You should not feel any discomfort. A heating pad might be used to keep your hand warm throughout the test.

Blood Vessel Imaging will be performed using ultrasound. The investigator will gently hold the ultrasound tool against the skin at the front of your neck while they take several pictures of two of the main blood vessels that lead to the brain (1 on the front region of your neck, and 1 slightly closer to the jaw line). This technique is similar to what is used in hospitals to investigate the heart and blood vessels or to look at a baby during pregnancy. Ultrasound monitoring requires the use of water-soluble, hypoallergenic gel between the probe and the surface of the skin.

Arterial Stiffness will be measured using a small pressure pen held against the skin at several locations including the wrist, neck (1 near the middle of the neck and 1 closer towards your jawline), and groin. In addition, a small toe-clip will be placed on your left second toe.

Cognitive testing will involve several paper and pencil tasks conducted by the study investigator. For example, you will be asked to remember a list of words, draw objects, trace a trail on paper, and make decisions to solve problems. Some tasks are easy while others are more difficult. It is important to try your best, no matter how easy or challenging you may find them. It is possible that you may feel some anxiety around completing these tests; however you will have the opportunity to practice before hand and ask any questions you may have.

24 hour Ambulatory Blood Pressure Monitoring device will be sent home with you following your three laboratory testing sessions. This device will periodically inflate on your arm for a period of 24 hours during which time you are encouraged to go about your normal activities of daily living and avoid strenuous physical activity. The monitor will automatically inflate once every 30 minutes during the day-time and every hour at night-time.

Are there any special instructions I should follow when I come in to the lab?
Yes. On each day of **laboratory testing**, you are asked to:

- Not perform any ***strenuous*** physical activity for ***24 hours*** prior to the laboratory sessions
- Avoid caffeine, alcohol, and nicotine ***on the day of*** testing
- Eat only a light meal at least ***4 hours prior*** to the start of testing
- Bring with you a loose-fitting short sleeve shirt and shorts

You will be reminded before each laboratory testing of the requirements listed above.

Handgrip Training days (approximately 20 minutes):
Following the initial Laboratory Testing day, you will be randomly (by chance) allocated to be in 1 of 3 groups. Groups 1 and 2 will be asked to perform 3 handgrip exercise sessions per week, identical to the exercise performed during Visit 2 (four 2 minute squeezes, separated by 1 minute of rest, and alternating hands after each squeeze). Again, these will be performed at 30% of your hardest squeeze on each training day. Two out of 3 weekly training days will be performed at the Brock-Niagara Centre for Health and Well-Being or Brock University campus, while the remaining training day may be performed at home. On supervised exercise session days, your blood pressure and heart rate will be monitored before each session, and handgrip exercise will be supervised by an exercise trainer.

If you are in Group 3, you will still visit the centre twice each week to have your blood pressure and heart rate measured. In all groups we will monitor any changes in diet, exercise, and medication on a log sheet which will be provided to each participant and ask

that you sign the log at each visit to demonstrate that you still would like to be involved in the study.

Isometric handgrip exercise may result in some tendon soreness of the exercising limb. Measures are in place which minimize the likelihood of this happening such as alternating hands which perform the contractions. This training protocol has been approved by the American Heart Association and is shown to produce minimal increases in heart rate and blood pressure, even in hypertensive populations. These increases go away quickly and pose no health risk to you. If you experience an adverse reaction, emergency action plans are set in place and all researchers and assistant will be trained to safely handle the situation.

At the end of the 8 weeks of training (Groups 1 and 2), you will perform handgrip exercise for another 4 weeks. During the final 4 weeks of handgrip training, the number of sessions that you are required to perform each week may remain the same (3 sessions per week) or you may stop the exercise altogether. You will be notified how many sessions you will be required to complete. Each week, your resting and ambulatory blood pressure will be monitored. Finally, at the end of the final 4 week period, you will have a final testing day at Brock University (**Welch Hall, room #22**) followed by 24 hour ambulatory blood pressure measurement.

Will I benefit from this study?

You may or may not experience a lower blood pressure at rest or during your activities of daily living after each part of the study. If handgrip training lowers blood pressure in the people in this study, it may be used by other individuals if their blood pressure is higher than it should be despite taking multiple blood pressure medications.

The handgrip training may result in improved arterial stiffness, short and long-term blood pressure regulation, and cognitive function. While these potential improvements may not be noticeable to you in your daily life, they have a large impact on your cardiovascular health over time.

You will be provided with feedback concerning the average responses of all participants as soon as possible following the completion of the study. A full summary of the study can be made available to all participants within 8 to 10 months following the conclusion of the testing period.

Will I be rewarded for volunteering my time?

You will be provided with free parking on Brock University premises during all laboratory based testing sessions. Secondary monetary compensation will not be provided.

Can I withdraw from the study?
Yes. Your participation in this study is completely voluntary. **You may withdraw from the study without penalty or any consequences at any time** by making the researchers aware of your decision. Should you choose to withdraw, the confidentiality of your involvement in the study will be maintained and data will be confidentially destroyed. If you do choose to withdraw, in most cases we will ask to use any data collected up to the time of your withdrawal, but you can request that any and all of your data be destroyed, again without consequence.

Your participation, or lack thereof, in this study will in no way influence your ability to participate in future studies at the Brock-Niagara Centre for Health and Well-Being or Brock University. The investigators may withdraw you from this research if circumstances arise which warrant doing so. Typically, this may occur due to change in medication, nutrition, or physical activity status.

How confidential and secure is my personal information?
Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will not be disclosed at any point in time without your expressed permission. Data will be retained for a period of 5 years following the completion of this study.

To ensure full confidentiality, following your consent, you will be assigned an identification code that can only be linked back to your data by an assigned study investigator. When the data are published in scientific journals or presented at research conferences, they will be expressed as group averages. In the event that individual data will be highlighted, the identification of that person will not be revealed. All paper data will be stored in a locked laboratory cabinet in Welch Hall at Brock University only accessible by study investigators. Digital information will be password protected. All information including medical questionnaires which contain personal identifiers will be destroyed if you choose to withdraw from the study.

Has this study received ethics clearance?
This project has been reviewed and received ethics clearance through the Brock University Bioscience Research Ethics Board (15 - 065).

We would like to remind you that if you have any questions, you may contact us at any time. Our contact information is on the first and last pages of this letter. Thank you for considering our study.

Sincerely,

Dr. Deborah O'Leary and Kylie Dempster
Department of Health Sciences, Brock University
905-688-5550 ext. 4339

Appendix B

CONSENT FORM

Study Title:

Influence of Isometric Handgrip Exercise Training on Cardiovascular and Cognitive Health in Hypertension

Researchers and Contact Information:

Deborah O'Leary, PhD phone: 905-688-5550 ext 4339 e-mail: doleary@brocku.ca
Kylie Dempster, BSc phone: 905-688-5550 ext 4593 e-mail: kd10dx@brocku.ca
Dept of Health Science, Faculty of Applied Health Sciences, Brock University, St Catharines, ON, L2S 3A1.Brock Niagara Centre for Health and Well-Being, 130 Lockhart Drive, St Catharines, ON, L2T 1W5.

Collaborators

Cheri McGowan, PhD phone: 519-253-3000 ext. 2451 e-mail: mcgowanc@uwindsor.ca

Your participation will remain confidential. The personal data collected from this investigation will be kept secured on the premises of Brock University in Dr. O'Leary's office or laboratory, and will not be accessed by anyone other than the listed investigators.

Investigators will require disclosure of your name and contact information (phone, email), and therefore your participation is not anonymous during the conduct of the research. However, all participants will have their names removed from any data. The master list matching participants to data will be kept by Kylie Dempster (student PI) in a secured room.

I have read the information presented in the information letter about the procedures and risks involved in this study. I have had the opportunity to ask any questions related to the study and have received satisfactory answers. I am aware that I may withdraw from the study without penalty at any time by making the researchers aware of this decision. If I have any further questions about participation in this study I know that I may contact Kylie Dempster, BSc, by phone at 905-688-5550 ext 4593, or by e-mail at kd10dx@brocku.ca or Deborah O'Leary, PhD, by phone at 905-688-5550, ext. 4339, or by e-mail at doleary@brocku.ca.

With full knowledge I agree, on my own free will, to be a participant in the research project identified above. I am aware that by signing the consent form, I am not waiving my legal rights or releasing the investigator(s) or involved institution(s) from their legal and professional responsibilities.

_____	_____
Participant (print name)	Participant (signature)
_____	_____
Witness (print name)	Witness (signature)
_____	_____
Date	Location

Appendix C

Medical and Educational History Questionnaire

Personal Information:

Height:_____ Weight:_____ Date of Birth:_____ Ethnicity:_____ Sex: M / F

Phone: (___)_____ Postal Code:_____

Emergency Contact Information:

Name:_____ Relation:_____

Address:_____

Phone:(___)_____

Medical Background:

Please circle Yes or No for each of the following questions:

1. Have you ever been hospitalized? Yes No
   If yes, please specify._____
   Have you ever had surgery? Yes No
   If yes, please specify.
   _____

2. Are you presently taking any medications or pills (including aspirin, and other over the counter medications)?
   Yes No
   If yes, please specify.
   _____

Medication name	Dose	Frequency

Are you presently taking any vitamins, supplements, and/or herbal supplements?
Yes No

3. Do you have any allergies (medicine, food, bees)? Yes No
   If yes, please specify.
   _____

4. Have you ever passed out during or after exercise? Yes No
   Have you ever been dizzy during or after exercise? Yes No
   Have you ever had chest pain during or after exercise? Yes No
   Do you have high blood pressure (hypertension) or low blood pressure (hypotension)?
   Yes No
   Have you ever been told that you have a kidney problem? Yes No
   Have you ever been told that you have joint instability? Yes No
   Have you ever been told that you have a stomach problem? Yes No
   Have you ever been told that you have a heart problem? Yes No
   Have you ever been told that you have a heart murmur? Yes No
   Do you have a machine that regulates your heart rate (pacemaker)? Yes No
   Have you ever had racing of your heart or skipped beats? Yes No
   Has anyone in your family died of heart disease or sudden death before age 50?
   Yes No

5. Do you have Diabetes? Yes No

6. Do you have asthma or any other breathing related problems? Yes No
   If yes, please specify:
   _____

7. Do you have any type of cardiovascular disease? Yes No
   If yes, please specify:
   _____

8. Have you had any other medical problems? Yes No
   If yes, please specify:
   _____

9. Have you had any medical problems since your last physical examination? Yes No

10. Do you currently smoke? Yes No
    Have you ever smoked? Yes No
    If yes, specify date of smoking cessation:
    _____

11. Do you exercise >30 minutes on ≥2 days per week? Yes No
    If yes, please describe your activities
    _____

Exercise	Duration (mins)	Frequency	Intensity

12. Are you currently pre-, peri-, or post-menopausal? (Answer *post-menopausal* if your last menstrual period was over *one* year ago). Please circle the most appropriate response.
    Pre-menopausal Peri-menopausal Post-menopausal

13. If post-menopausal, at what age did you consider yourself menopausal?

    _____

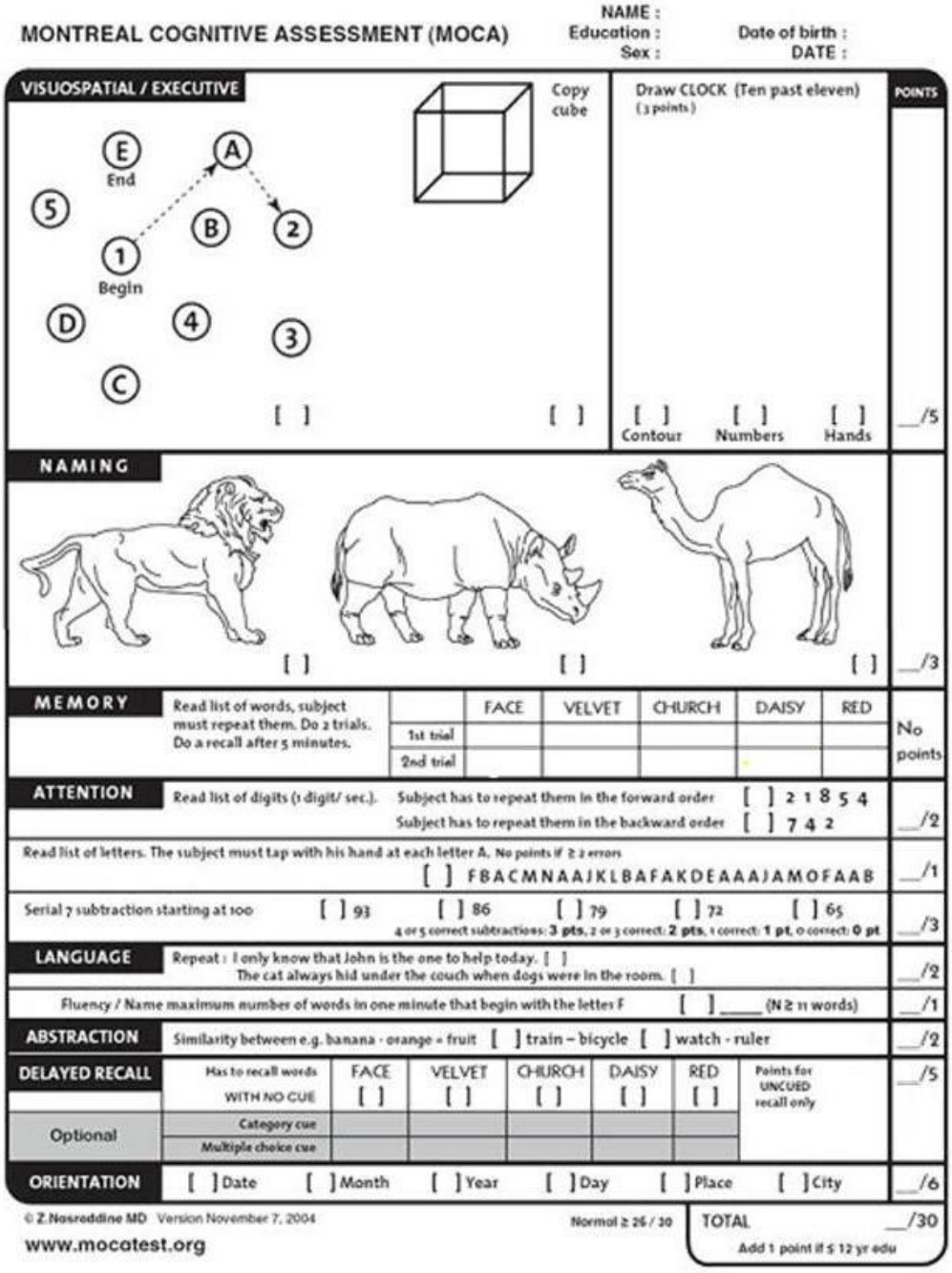
14. Did you in the past, or do you currently take hormone replacement therapy?
    Yes I am currently on HRT
    Yes I have taken HRT but do not currently
    No I have never taken HRT

Educational Background:

Please circle the highest educational ranking achieved:

a) High School Diploma
b) College Degree (2 years)
c) University Degree (4 years)
d) Graduate Degree (Master's and/or Doctorate)

Appendix D



MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ]

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION — [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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Normal ≥ 26 / 30

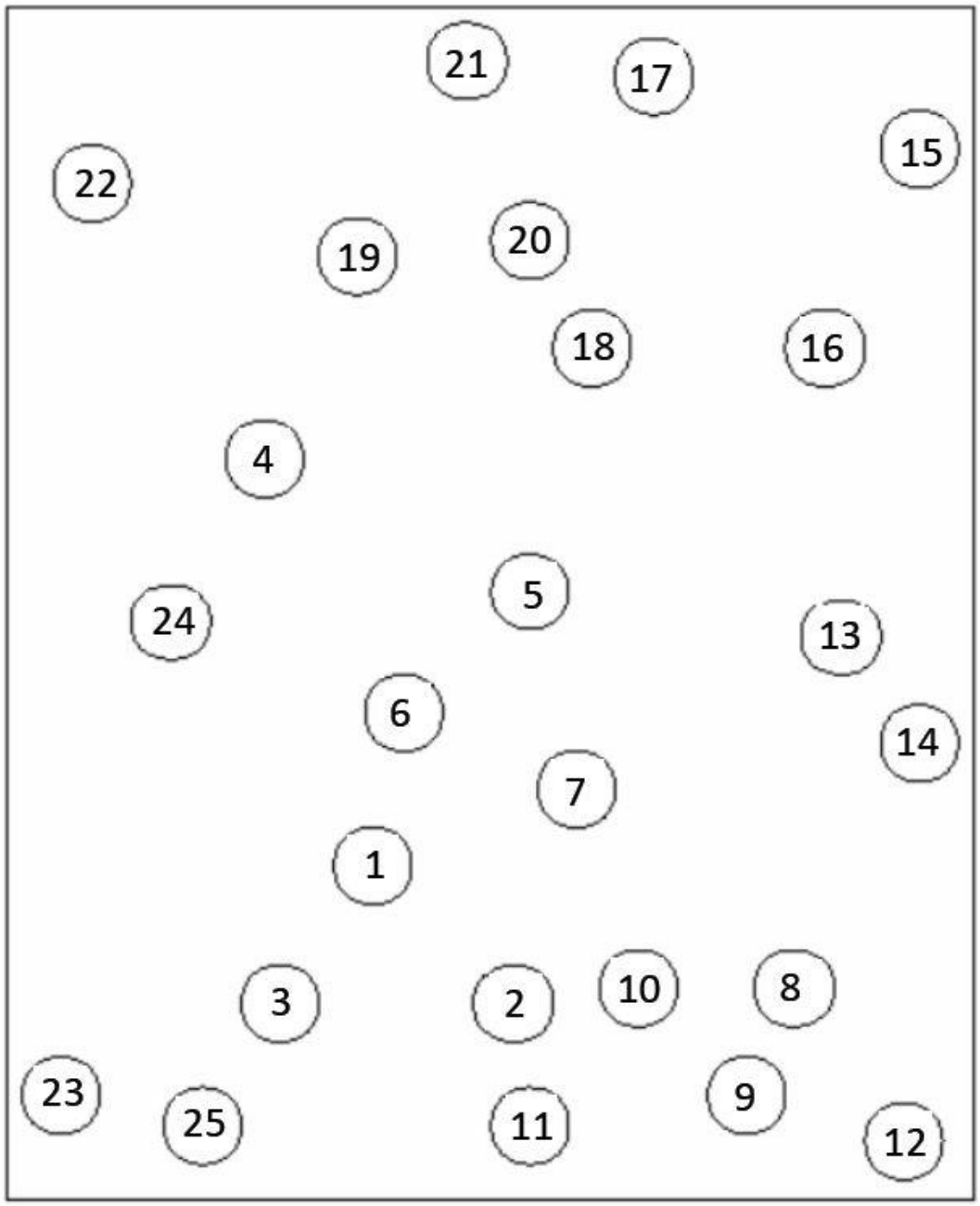
TOTAL __/30

Add 1 point if ≤ 12 yr edu

Appendix E

Trail Making Test Part A

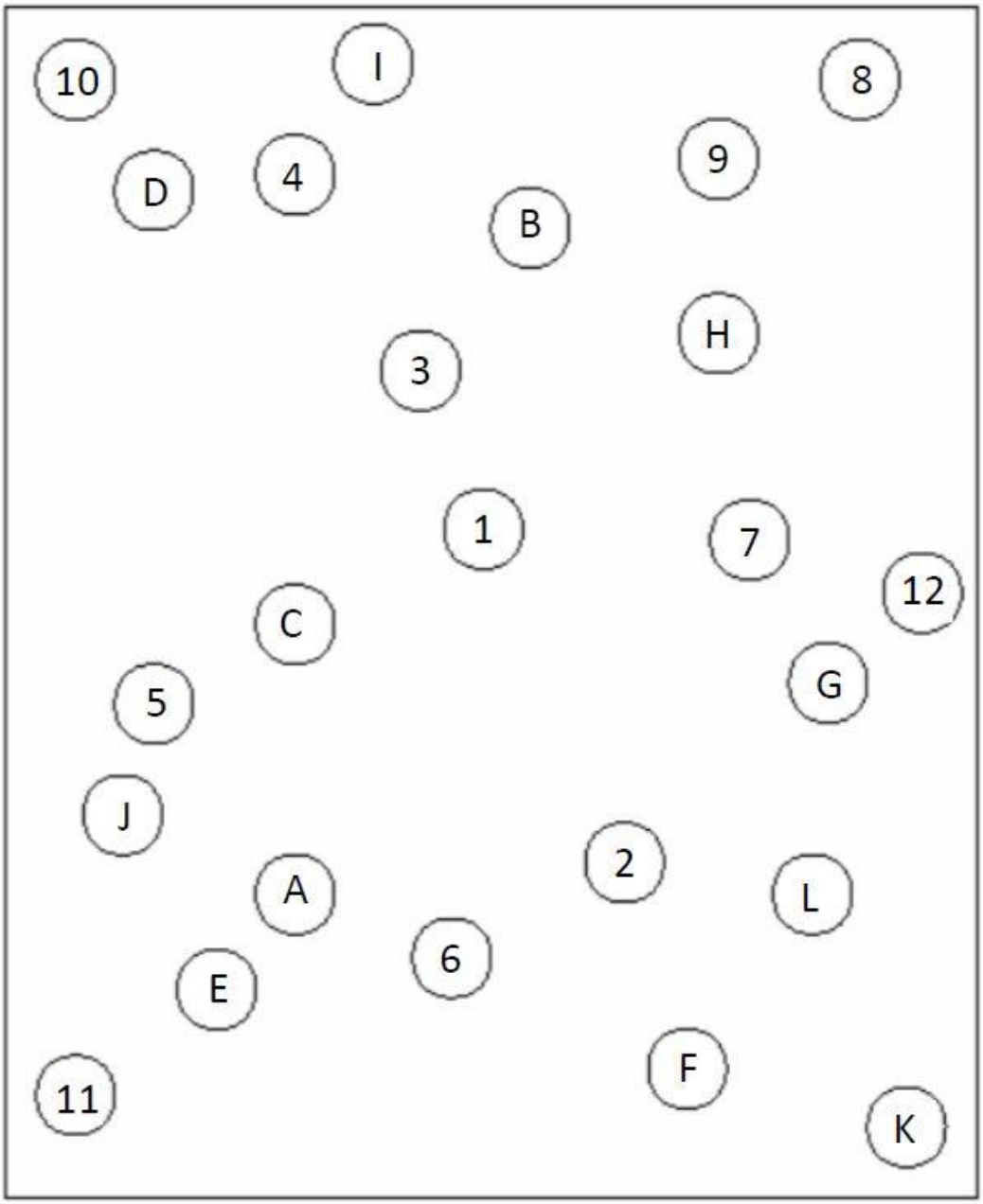
Patient's Name: _____ Date: _____



Appendix F

Trail Making Test Part B

Patient's Name: _____ Date: _____



Appendix G

Centre for Epidemiological Studies Depression Scale

Place a check mark (✓) in the appropriate column. During the past week...	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	All of the time (5-7 days)
1. I was bothered by things that usually don't bother me.				
2. I did not feel like eating; my appetite was poor.				
3. I felt that I could not shake off the blues even with help from my family.				
4. I felt that I was just as good as other people.				
5. I had trouble keeping my mind on what I was doing.				
6. I felt depressed.				
7. I felt that everything I did was an effort.				
8. I felt hopeful about the future.				
9. I thought my life had been a failure.				
10. I felt fearful.				
11. My sleep was restless.				
12. I was happy.				
13. I talked less than usual.				
14. I felt lonely.				
15. People were unfriendly.				
16. I enjoyed life.				
17. I had crying spells.				
18. I felt sad.				
19. I felt that people disliked me.				
20. I could not "get going."				

During the past week...	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	All of the time (5-7 days)	Score
1. I was bothered by things that usually don't bother me.	0	1	2	3	
2. I did not feel like eating; my appetite was poor.	0	1	2	3	
3. I felt that I could not shake off the blues even with help from my family.	0	1	2	3	
4. I felt that I was just as good as other people.	3	2	1	0	
5. I had trouble keeping my mind on what I was doing.	0	1	2	3	
6. I felt depressed.	0	1	2	3	
7. I felt that everything I did was an effort.	0	1	2	3	
8. I felt hopeful about the future.	3	2	1	0	
9. I thought my life had been a failure.	0	1	2	3	
10. I felt fearful.	0	1	2	3	
11. My sleep was restless.	0	1	2	3	
12. I was happy.	3	2	1	0	
13. I talked less than usual.	0	1	2	3	
14. I felt lonely.	0	1	2	3	
15. People were unfriendly.	0	1	2	3	
16. I enjoyed life.	3	2	1	0	
17. I had crying spells.	0	1	2	3	
18. I felt sad.	0	1	2	3	
19. I felt that people disliked me.	0	1	2	3	
20. I could not "get going."	0	1	2	3	
				Total Score:	

Appendix H

Power Calculation

Statistical power was calculated to detect a significant change in SBP following IHG training according to a recent review specifically examining cardiovascular adaptations to IHG training.[15] SBP was selected due to its consistent association with arterial stiffness, BRS, and cognitive function.[7,14,76] This review identified average adaptations to IHG training across all studies to be approximately 10-13 mmHg, depending on the population selected.[15] As we were interested in hypertensive individuals who often experienced larger reductions in BP in response to IHG training, a difference of 13 mmHg was selected for our power calculation. Significance was set to $\alpha = 0.05$ in order to calculate a required sample size for detecting the 13 mmHg difference in SBP for power values ranging from 0.6 – 0.9. The results of this calculation are presented below. It was determined that a sample size of 8 participants in the IHG group would be required to achieve 80% power based upon previously established reports.

Power Calculation

Nominal Power	Actual Power	Sample size
0.6	0.642	6
0.7	0.741	7
0.8	0.817	8
0.9	0.913	10